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Facile synthesis of acridines *via* Pd(0)-diphosphine complex-catalyzed tandem coupling/cyclization protocol†

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A facile and efficient approach for the synthesis of a variety of acridines *via* the tandem coupling/cyclization of substituted 2-bromobenzaldehydes and anilines is described. The reaction can be accomplished with ease in the presence of a catalytic amount of $Pd_2(dba)_3$ and diphosphine ligand dppf, providing a broad range of substituted acridines in good to excellent yields (up to 99%). The Lewis acid, $AlCl_3$, is required to promote the cyclization for less electron-rich anilines.

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Introduction

Acridines are an important class of biologically active compounds that have been widely used as antibacterial, antiprotozoal and antileukemic agents, as well as anticancer drugs, mainly owing to their inhibition of DNA-related enzymes, such as topoisomerases, by intercalation.[1] Among the bioactive acridines, porflavine,[2,3a] euflavine,[3] aminacrine,[4a,b] and ethacridine[4b–d] are already approved as antibacterial drugs and have been in use for many years, whereas m-AMSA[5] and DACA[6] are two representative anticancer agents that have been in clinical trials for the treatment of leukemia (Fig. 1).

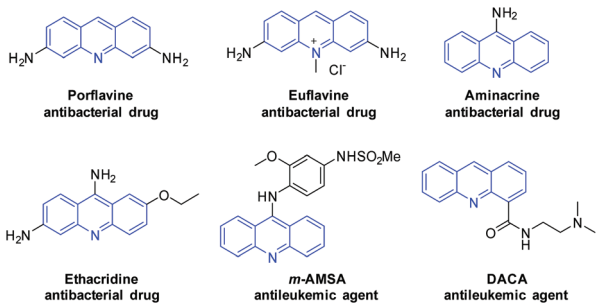

Fig. 1 Representative bioactive acridines.

Owing to their importance in human medicines and many other applications, considerable effort has been devoted to developing efficient synthetic methodologies for the construction of acridines over the past decades.[7–13] One of the earliest methods, the Bernthsen reaction between diphenylamine and carboxylic acids, needs a high temperature (200–270 °C) to furnish acridine products.[7] Other reported methodologies have mainly focused on strategies such as C–H functionalization,[8] reduction,[9] dehydration,[10] intermolecular annulation,[11] and intramolecular cyclization.[12] However, those methods are often limited in scope and generally require harsh, functional group-intolerant conditions.[13] Very recently, an interesting Pd(II)-catalyzed one-pot reaction was reported for constructing acridines from 2-formylphenyl triflates and aniline substrates, but only three examples of electron-rich anilines were presented and electron-poor anilines did not undergo the reaction.[11e] Moreover, the triflate group was essential and almost no reaction was found to occur with commercially available 2-bromobenzaldehyde as the substrate. In this regard, there is still a lack of efficient methods for the synthesis of acridines; therefore, the development of a new practical approach with broad substrate scope is of great importance and highly desirable. Herein, we describe our findings on the tandem coupling/cyclization reaction of easily accessed substituted 2-bromobenzaldehyde and a wide range of anilines to afford various acridines.

Results and discussion

As part of our ongoing interest in intramolecular aza-Friedel–Crafts reactions,[14] we initially attempted to synthesize *o*-aminobenzaldehyde **4a** through the coupling reaction of 2-bromobenzaldehyde (**1a**) and 3,5-dimethoxyaniline (**2a**) under

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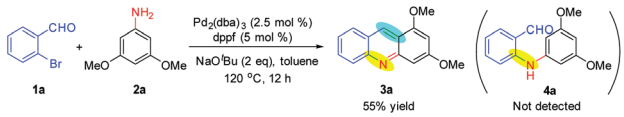


Scheme 1 Initial discovery of the formation of the acridine product.

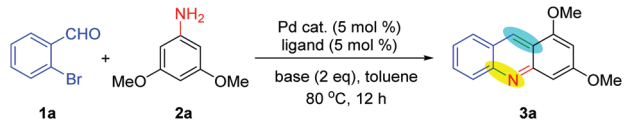
palladium catalysis (Scheme 1). Surprisingly, acridine **3a** was isolated in 55% yield instead of desired amination product **4a**. This result indicates that the reaction undergoes a smooth one-pot coupling/cyclization process. In contrast to the previously reported method that is limited to the use of triflates, we expected that this transformation could provide a more simple, economical and efficient approach for accessing diversely substituted acridines.

To improve the reaction efficiency, we began our investigation by optimizing the reaction conditions (Table 1). Lowering the reaction temperature to 80 °C only led to a slight decrease in the yield of **3a** (entry 2), suggesting that the reaction is relatively unaffected by temperature. We found that the desired acridine product could be obtained in 81% yield when KOH was used as the base (entry 3). Further screening of bases indicated that K_2CO_3 was the best choice, affording target acridine **3a** in almost quantitative yield (entry 5). Different palladium precursors and phosphine ligands did not give better results (entries 6–11). It is worth noting that the bi-dentate phosphine ligand is probably essential for the reaction because almost no product was detected in the presence of monophosphine ligands such as X-Phos and PPh_3 (entries 10 and 11). Changing the solvent from toluene to DMF or dioxane decreased the yield (entries 12 and 13). Moreover, the most suitable ratio of [Pd]/L was 1 : 1 (entries 5 *vs.* 14 and 15). Therefore, the optimal conditions were determined to be 2.5 mol% $Pd_2(dba)_3$, 5 mol% dppf, and 2 equiv. K_2CO_3 in toluene at 80 °C (entry 5).

With the optimal reaction conditions established, we began to explore the substrate generality. Firstly, a variety of 2-bromobenzaldehydes bearing different substituents were examined. The results are summarized in Table 2. To our delight, 2-bromobenzaldehydes containing either electron-donating or electron-withdrawing groups could be successfully applied, providing expected acridine products **3b–h** in good to excellent yields (85–99%). Notably, the analogous cyclization of electron-deficient 2-formylphenyl triflates with 3,5-dimethoxyaniline only gave low yields of **3b** (32%) and **3d** (59%) with a prolonged reaction time.[11e] In addition, 4, 5 or 6-fluoro-substituted 2-bromobenzaldehydes reacted smoothly to produce acridines **3h**, **3c** and **3i** in excellent yields (85–99%). For substrate **1j**, which contained a methoxy group *ortho* to the bromine, a lower yield (**3j**, 59%) was obtained, probably because of the increased steric hindrance during amination.

Next, we investigated the substrate scope of anilines. The yields decreased significantly when 3,5-dimethoxyaniline **2a**

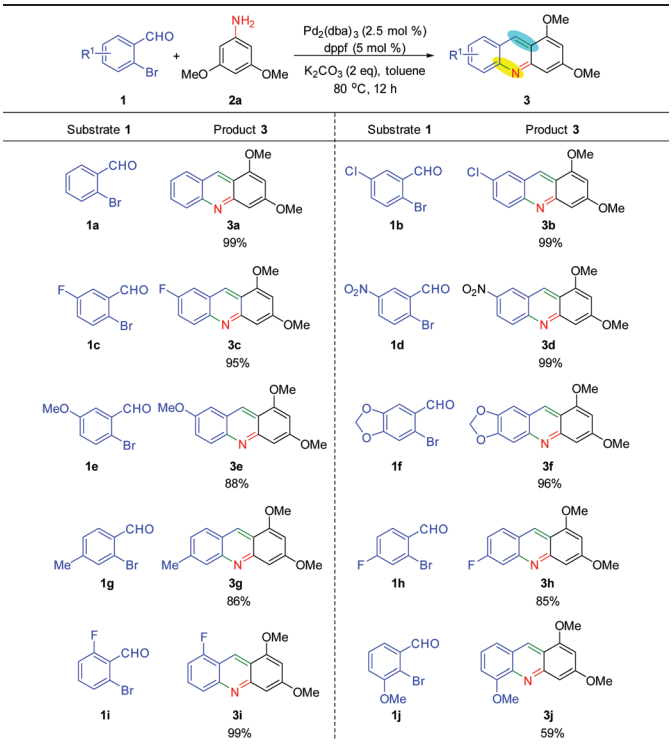
Table 1 Optimization of the reaction conditions[a]



Entry	Pd cat.	Ligand	Base	Solvent	Yield[b] (%)
1[c]	$Pd_2(dba)_3$	dppf	NaO^{t}Bu	Toluene	55
2	$Pd_2(dba)_3$	dppf	NaO^{t}Bu	Toluene	49
3	$Pd_2(dba)_3$	dppf	KOH	Toluene	81
4	$Pd_2(dba)_3$	dppf	K_3PO_4	Toluene	47
5	$Pd_2(dba)_3$	dppf	K_2CO_3	Toluene	99
6	$Pd(OAc)_2$	dppf	K_2CO_3	Toluene	23
7	$PdCl_2$	dppf	K_2CO_3	Toluene	41
8	$Pd_2(dba)_3$	dppb	K_2CO_3	Toluene	22
9	$Pd_2(dba)_3$	BINAP	K_2CO_3	Toluene	81
10	$Pd_2(dba)_3$	X-Phos	K_2CO_3	Toluene	Trace
11	$Pd_2(dba)_3$	PPh_3	K_2CO_3	Toluene	Trace
12	$Pd_2(dba)_3$	dppf	K_2CO_3	DMF	72
13	$Pd_2(dba)_3$	dppf	K_2CO_3	Dioxane	89
14[d]	$Pd_2(dba)_3$	dppf	K_2CO_3	Toluene	93
15[e]	$Pd_2(dba)_3$	dppf	K_2CO_3	Toluene	87

[a] Reactions were performed with 0.24 mmol of aldehyde **1**, 0.2 mmol of aniline **2** in the presence of 5 mol% of Pd catalyst and 2 equiv. of base in 2 mL of dry toluene at 80 °C. [b] Isolated yield. [c] 120 °C. [d] [Pd]/L = 1/2. [e] [Pd]/L = 2/1.

Table 2 Reaction of 2-bromobenzaldehydes **1** with 3,5-dimethoxyaniline (**2a**)[a,b]



[a] Reactions were performed with 0.2 mmol of 3,5-dimethoxyaniline **2a**, 0.24 mmol of substituted 2-bromobenzaldehyde **1**, 2.5 mol% of $Pd_2(dba)_3$, 5 mol% of dppf, and 2 equiv. K_2CO_3 in 2 mL of dry toluene at 80 °C. [b] Isolated yield.

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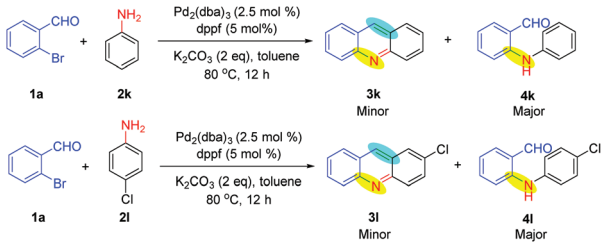


Scheme 2 Reaction with less electron-rich anilines.

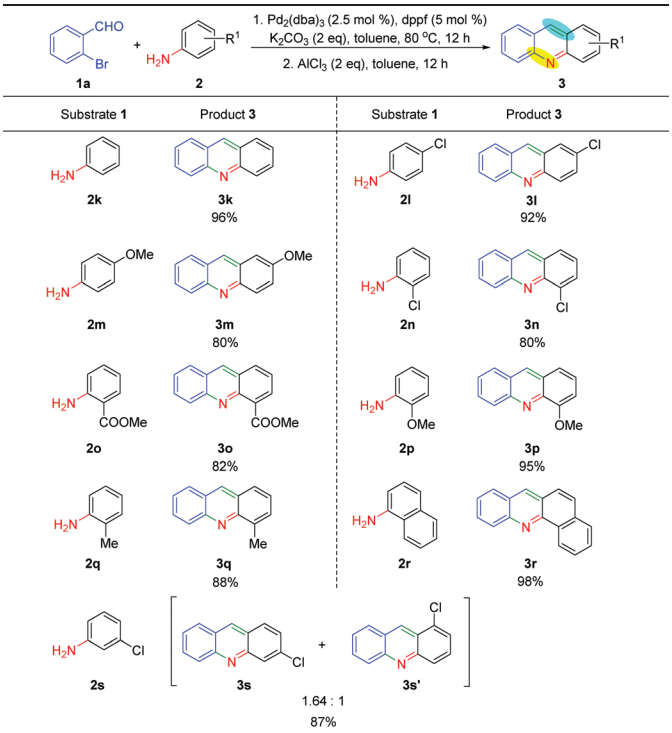
was changed to electron-neutral aniline **2k** or electron-deficient aniline **2l**. Unsurprisingly, the C–N coupling product (**4k** and **4l**) was mainly obtained (Scheme 2). Considering the Friedel–Crafts cyclization mechanism, we speculate that the presence of a Lewis acid may activate the aldehyde carbonyl, thus favoring electrophilic attack by a less electron-rich aniline.

We were excited to find that the use of $AlCl_3$ as a Lewis acid dramatically promoted the formation of acridine. For example, desired acridine **3k** could be obtained in very good yield (96%) by treatment of the crude amination product **4k** with 2 equiv. of $AlCl_3$ in toluene at 80 °C for 12 h. Interestingly, the cyclization also proceeded when $AlCl_3$ (2 equiv.) was added to the reaction mixture after the amination step; however, a generally lower yield (90% for **3k**) was obtained, probably because of the effect of the palladium species. With the optimized reaction sequence (Pd-catalyzed coupling conditions followed by $AlCl_3$/toluene), a series of less electron-rich anilines substituted with substituents, including chloro (**2l**, **2n**, **2s**), ester (**2o**), methoxy (**2m**, **2p**), and methyl (**2q**) groups, were tested (Table 3). In all cases, good to excellent yields were attained. Notably, acridine **3o**, the crucial intermediate for the synthesis of antileukemic agent DACA,[6] could be readily accessed in high yield (82%),[15] whereas previous syntheses required three to four steps, sometimes under harsh conditions.[6a–c] Furthermore, 1-naphthylamine with higher steric hindrance can be used for this transformation, giving otherwise difficult-to-access **3r** in excellent yield (98%). Meanwhile, aniline with *meta*-substitution was also compatible, although it produced regioisomers of acridines **3s** and **3s′** with a ratio of 1.64 : 1 in favor of **3s**.

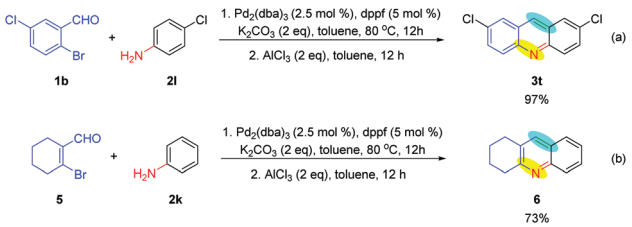
To extend the substrate scope of this method further, the reaction between two electron-poor components of aldehyde **1b** and aniline **2l** was examined (Scheme 3a). Symmetrical dichloro-substituted acridine **3t** was obtained in excellent yield (97%). The two halogen substituents on the benzene ring could be useful functionalities for further elaboration through coupling reactions. We also tested the reaction of 2-bromocyclohexene-1-carbaldehyde (**5**) with aniline **2k** (Scheme 3b). Under the same conditions, we found that the core structure of cholinesterase inhibitor tacrine,[16] 1,2,3,4-tetrahydroacridine **6**, could be easily constructed in 73% yield.

In the preliminary investigation of the reaction mechanism, we found that the aldehyde functionality played a vital role in the amination step. Under standard conditions, the coupling

Table 3 Reaction of 2-bromobenzaldehyde with less electron-rich anilines[a,b]



[a] See Experimental section for details. [b] Isolated yield.



Scheme 3 Extension of the substrate scope.

reaction between bromobenzene (**7**) and aniline **2a** hardly proceeded, and mainly **2a** was recovered (Scheme 4). This result suggests that the *ortho*-formyl group might be involved in stabilizing the assumed palladacycle intermediate.

Based on these results and previous reports,[12d,17,18] a plausible mechanism for this tandem reaction is shown in Fig. 2. Initially, substituted 2-bromobenzaldehyde **1** undergoes oxidative addition to the Pd(0) species to form complex **A**, which is converted to intermediate **C** through transition state **B**. The following reductive elimination yields amination product **4**, completing the palladium catalysis cycle. Subsequently, the formyl carbonyl is attacked by the aromatic ring in the presence/absence of a Lewis acid, promoting the formation of cyclization intermediate **E** from **D**. Finally, acridine product **3** is obtained after Lewis acid dissociation and dehydration.

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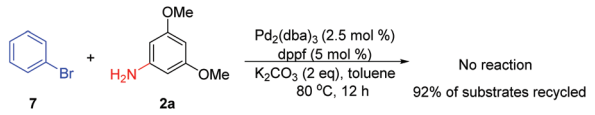

Scheme 4 Amination with simple bromobenzene **7**.

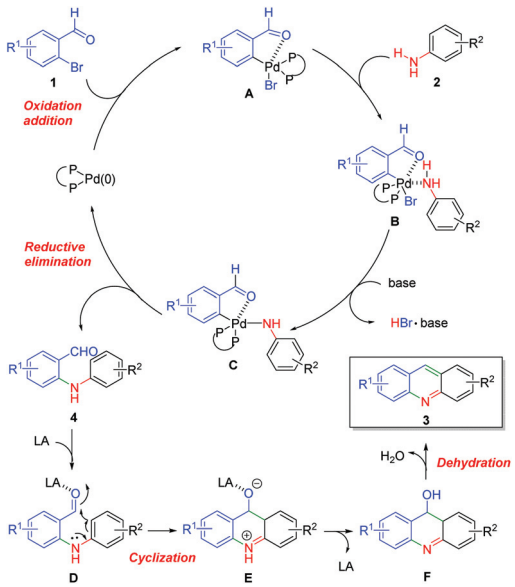

Fig. 2 Proposed reaction mechanism.

Conclusions

In summary, we have demonstrated an efficient tandem coupling/cyclization approach for facile synthesis of diversely substituted acridines. The reaction could be accomplished with ease under Pd(0)-catalysis by using readily available 2-bromobenzaldehydes and anilines as starting materials. The Lewis acid $AlCl_3$ is required to promote the sequential cyclization for less electron-rich anilines. The method allows the construction of a broad range of symmetrical and unsymmetrical acridines bearing multifunctional substituents, as well as the unusual 1,2,3,4-tetrahydroacridine in good to excellent yields (up to 99%). Moreover, antileukemic agent DACA can be easily accessed in just two simple linear steps using our method. We believe that this work provides further opportunities for extensive future applications of acridines in medicinal chemistry, organic synthesis and material science.

Experimental

General methods

All reactions were carried out in dry glassware with magnetic stirring. Solvents were dried and distilled by standard procedures. NMR spectra were recorded on a spectrometer (300 MHz for ^{1}H, and 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^{1}H NMR and chloroform-d (δ 77.36) for ^{13}C NMR. MS and HRMS were measured in ESI mode, and a Q-TOF mass analyzer was used for HRMS.

General procedure for the tandem coupling/cyclization reaction of substituted *o*-bromobenzaldehyde with 3,5-dimethoxyaniline

Under an N_2 atmosphere, a reaction vessel was charged sequentially with 3,5-dimethoxyaniline **2a** (0.2 mmol), $Pd_2(dba)_3$ (0.005 mmol), dppf (0.01 mmol), K_2CO_3 (0.4 mmol) and freshly distilled toluene (1.0 mL). The mixture was stirred for 5 min at room temperature then a solution of substituted 2-bromobenzaldehyde **1** (0.24 mmol) in freshly distilled toluene (1.0 mL) was added. The reaction mixture was heated at 80 °C for 12 h before being cooled to room temperature and quenched with water (5 mL). The aqueous phase was extracted with ethyl acetate (10 mL × 3) and the combined organic phase was washed with brine then dried over Na_2SO_4. The residue obtained after filtration and concentration was purified by flash column chromatography (eluent: petroleum ether/acetone = 10/1 to 1/1) to afford desired acridine product **3**.

General procedure for reaction of substituted 2-bromobenzaldehyde with less electron-rich anilines

Under an N_2 atmosphere, a reaction vessel was charged with aniline **2** (0.24 mmol), $Pd_2(dba)_3$ (0.005 mmol), dppf (0.01 mmol), K_2CO_3 (0.4 mmol) and freshly distilled toluene (1.0 mL). The solution was stirred for 5 min at room temperature, and then a solution of substituted 2-bromobenzaldehyde **1** (0.2 mmol) in freshly distilled toluene (1.0 mL) was added. The reaction mixture was heated at 80 °C for 12 h, and then cooled to room temperature and filtered through Celite. The filtrate was concentrated under reduced pressure and $AlCl_3$ (0.4 mmol) followed by freshly distilled toluene (2.0 mL) was added to the residue. The mixture was heated at 80 °C for another 12 h before being cooled to room temperature and quenched with water (5 mL). The aqueous phase was extracted with ethyl acetate (10 mL × 3) and the combined organic phase was washed with brine and dried over Na_2SO_4. The residue was filtered and concentrated under reduced pressure and was purified by flash column chromatography (eluent: petroleum ether/ethyl acetate = 20/1 to 10/1) to give acridine product **3**. 1,2,3,4-Tetrahydroacridine **6** was synthesized with the same procedure.

1,3-Dimethoxyacridine (3a).[11e] Yellow solid (47.6 mg, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.74 (ddd, J_1 = 8.0 Hz, J_2 = 7.7 Hz, J_2 = 1.5 Hz, 1H), 7.45 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.06 (d, J = 1.5 Hz, 1H), 6.42 (d, J = 2.1 Hz, 1H), 4.02 (s, 3H), 3.98 (s, 3H).

7-Chloro-1,3-dimethoxyacridine (3b).[11e] Yellow solid (54.3 mg, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.03 (d, J = 9.3 Hz, 1H), 7.92 (s, 1H), 7.65 (dd, J_1 = 9.3 Hz, J_2 = 2.1 Hz, 1H), 7.03 (s, 1H), 6.45 (s, 1H), 4.03 (s, 3H), 3.98 (s, 3H).

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7-Fluoro-1,3-dimethoxyacridine (3c). Yellow solid (48.9 mg, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.11 (dd, J_1 = 10.2 Hz, J_2 = 5.4 Hz, 1H), 7.58–7.51 (m, 2H), 7.04 (d, J = 1.8 Hz, 1H), 6.45 (d, J = 1.8 Hz, 1H), 4.03 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 159.4 (d, J_{C-F} = 245.6 Hz), 156.1, 150.8, 146.9, 131.2 (d, J_{C-F} = 8.9 Hz), 130.9 (d, J_{C-F} = 6.6 Hz), 125.1 (d, J_{C-F} = 9.9 Hz), 122.1 (d, J_{C-F} = 27.0 Hz), 118.0, 110.8 (d, J_{C-F} = 21.3 Hz), 98.4, 98.2, 56.2, 56.1; ESI-MS (m/z, %) 258 $[M + H]^+$; ESI-HRMS calcd for $C_{15}H_{13}O_2NF$ $[M + H]^+$ 258.0925, found 258.0932.

1,3-Dimethoxy-7-nitroacridine (3d).[11e] Yellow solid (57.1 mg, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.85 (d, J = 2.4 Hz, 1H), 8.40 (dd, J_1 = 9.3 Hz, J_2 = 2.4 Hz, 1H), 8.08 (d, J = 9.6 Hz, 1H), 7.01 (d, J = 1.8 Hz, 1H), 6.45 (d, J = 1.8 Hz, 1H), 4.04 (s, 3H), 4.00 (s, 3H).

1,3,7-Trimethoxyacridine (3e).[11e] Yellow solid (47.6 mg, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.06 (d, J = 9.3 Hz, 1H), 7.45 (dd, J_1 = 9.3 Hz, J_2 = 2.7 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.08 (s, 1H), 6.45 (s, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.95 (s, 3H).

7,9-Dimethoxy-[1,3]dioxolo[4,5-*b*]acridine (3f). Yellow solid (54.5 mg, 96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.31 (s, 1H), 7.08 (s, 1H), 6.96 (s, 1H), 6.37 (s, 1H), 6.06 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 156.2, 152.5, 149.7, 148.7, 147.2, 129.7, 122.4, 116.1, 104.0, 102.7, 102.0, 98.1, 97.3, 56.1, 55.9; ESI-MS (m/z, %) 284 $[M + H]^+$; ESI-HRMS calcd for $C_{16}H_{14}O_4N$ $[M + H]^+$ 284.0917, found 284.0925.

1,3-Dimethoxy-6-methylacridine (3g). Yellow solid (43.6 mg, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.87 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.27 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 7.04 (d, J = 1.8 Hz, 1H), 6.38 (d, J = 2.1 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 156.6, 151.2, 149.9, 141.4, 131.4, 128.7, 127.5, 127.1, 123.5, 117.2, 98.2, 97.5, 56.1, 56.0, 22.6; ESI-MS (m/z, %) 254 $[M + H]^+$; ESI-HRMS calcd for $C_{16}H_{16}O_2N$ $[M + H]^+$ 254.1176, found 254.1179.

6-Fluoro-1,3-dimethoxyacridine (3h). Yellow solid (43.3 mg, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.93 (dd, J_1 = 9.0 Hz, J_2 = 6.3 Hz, 1H), 7.69 (dd, J_1 = 10.5 Hz, J_2 = 1.8 Hz, 1H), 7.28–7.22 (m, 1H), 7.02 (s, 1H), 6.42 (s, 1H), 4.02 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2 (d, J_{C-F} = 250.3 Hz), 163.2, 156.7, 151.9, 150.4 (d, J_{C-F} = 13.3 Hz), 131.9, 131.4 (d, J_{C-F} = 10.5 Hz), 122.4, 117.1, 116.4 (d, J_{C-F} = 26.9 Hz), 111.3 (d, J_{C-F} = 19.9 Hz), 98.1, 97.8, 56.2, 56.1; ESI-MS (m/z, %) 258 $[M + H]^+$; ESI-HRMS calcd for $C_{15}H_{13}O_2NF$ $[M + H]^+$ 258.0925, found 258.0928.

8-Fluoro-1,3-dimethoxyacridine (3i). Yellow solid (51.2 mg, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.69–7.62 (m, 1H), 7.10 (dd, J_1 = 9.9 Hz, J_2 = 7.8 Hz, 1H), 7.05 (d, J = 1.8 Hz, 1H), 6.46 (d, J = 2.1 Hz, 1H), 4.04 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 158.9 (d, J_{C-F} = 255.3 Hz), 156.7, 151.7, 150.1, 130.0 (d, J_{C-F} = 9.4 Hz), 125.6 (d, J_{C-F} = 4.3 Hz), 124.6 (d, J_{C-F} = 4.0 Hz), 117.5, 116.6 (d, J_{C-F} = 16.8 Hz), 107.4 (d, J_{C-F} = 19.1 Hz), 98.3, 98.2, 56.3, 56.1; ESI-MS (m/z, %) 258 $[M + H]^+$; ESI-HRMS calcd for $C_{15}H_{13}O_2NF$ $[M + H]^+$ 258.0925, found 258.0933.

1,3,5-Trimethoxyacridine (3j).[11e] Yellow solid (31.4 mg, 59%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.36 (dd, J_1 = 7.8 Hz, J_2 = 7.8 Hz, 1H), 7.26–7.25 (m, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.45 (d, J = 1.8 Hz, 1H), 4.13 (s, 3H), 4.02 (s, 3H), 3.97 (s, 3H).

Acridine (3k).[10] Light yellow solid (34.2 mg, 96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.25 (d, J = 9.0 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.79 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 2H), 7.54 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 2H).

2-Chloroacridine (3l).[11a] Light yellow solid (39.3 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.20 (dd, J_1 = 12 Hz, J_2 = 9.6 Hz, 1H), 8.00–7.97 (m, 2H), 7.82–7.77 (m, 1H), 7.69 (dd, J_1 = 9.3 Hz, J_2 = 2.4 Hz, 1H), 7.59–7.54 (m, 1H).

2-Methoxyacridine (3m).[12e] Yellow solid (33.4 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.20 (dd, J_1 = 8.7 Hz, J_2 = 0.6 Hz, 1H), 8.13 (d, J = 9.6 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.74–7.69 (m, 1H), 7.54–7.45 (m, 2H), 7.15 (d, J = 2.7 Hz, 1H), 3.97 (s, 3H).

4-Chloroacridine (3n).[12b] Light yellow solid (33.9 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.38 (dd, J_1 = 8.7 Hz, J_2 = 0.6 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.94–7.93 (m, 1H), 7.91 (s, 1H), 7.82 (ddd, J_1 = 8.0 Hz, J_2 = 7.6 Hz, J_2 = 1.5 Hz, 1H), 7.57 (ddd, J_1 = 7.6 Hz, J_2 = 7.4 Hz, J_2 = 0.9 Hz, 1H), 7.43 (dd, J_1 = 7.8 Hz, J_2 = 7.8 Hz, 1H).

Methyl acridine-4-carboxylate (3o).[6b] Brown oil (38.9 mg, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.30 (d, J = 9.0 Hz, 1H), 8.13 (d, J = 7.8 Hz, 2H), 8.00 (d, J = 8.4 Hz, 1H), 7.83–7.78 (m, 1H), 7.59–7.52 (m, 2H), 4.12 (s, 3H).

4-Methoxyacridine (3p).[12e] Brown solid (39.7 mg, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.40 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.79–7.74 (m, 1H), 7.59–7.52 (m, 2H), 7.45 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 4.16 (s, 3H).

4-Methylacridine (3q).[12e] Yellow solid (34.2 mg, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.29 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.79–7.74 (m, 1H), 7.62 (d, J = 6.6 Hz, 1H), 7.53 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 7.42 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 2.96 (s, 3H).

Benzo[*c*]acridine (3r).[12e] Light yellow solid (45.9 mg, 98%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (d, J = 8.4 Hz, 1H), 8.65 (s, 1H), 8.39 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.90–7.69 (m, 6H), 7.60 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H).

3-Chloroacridine (3s).[12e] Yellow solid (22.9 mg, 54%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.23 (s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.83–7.78 (m, 1H), 7.55 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 7.46 (dd, J_1 = 9.0 Hz, J_2 = 0.9 Hz, 1H).

1-Chloroacridine (3s′).[12e] Yellow solid (14.3 mg, 33%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.86–7.80 (m, 1H), 7.71–7.56 (m, 3H).

2,7-Dichloroacridine (3t). Light yellow solid (48.2 mg, 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.14 (d, J = 9.3 Hz, 2H), 7.95 (d, J = 2.1 Hz, 2H), 7.70 (dd, J_1 = 9.3 Hz, J_2 = 2.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 134.3, 132.6, 132.2,

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131.5, 127.3, 126.5; ESI-MS (*m*/*z*, %) 248 $[M + H]^+$; ESI-HRMS calcd for $C_{13}H_8NCl_2$ $[M + H]^+$ 248.0028, found 248.0026.

1,2,3,4-Tetrahydroacridine (6).[10] Yellow oil (26.8 mg, 73%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 1H), 7.80 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.63–7.58 (m, 1H), 7.43 (dd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, 1H), 3.13 (t, J = 6.6 Hz, 2H), 2.97 (t, J = 6.3 Hz, 2H), 2.04–1.96 (m, 2H), 1.93–1.85 (m, 2H).

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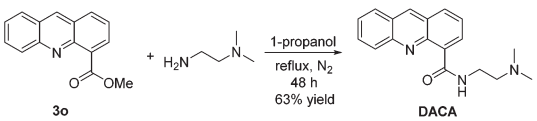

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