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DDQ promoted metal-free oxidative cascade synthesis of acridinyl ketones and 4-benzoylacridinones from C4-functionalized 1,2,3,4-tetrahydroacridines

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Herein, we report a DDQ-mediated, metal-free oxidative cascade protocol for the synthesis of acridin-4-yl(aryl)methanones and 4-benzoylacridin-9(10*H*)-ones (acridones) through sequential dehydrogenative aromatization and C(sp^2)–H oxidation of C4-substituted 1,2,3,4-tetrahydroacridines. With operational simplicity, mild reaction conditions, and no transition metals, this cascade offers a step-economical and metal-free approach to access acridine scaffolds. This method exhibits broad functional group tolerance in delivering the desired products in good yields. Mechanistic investigations, including radical-trapping and nucleophile-probing experiments, support a pathway initiated by hydrogen atom transfer (HAT), followed by a single electron transfer (SET), forming the key benzyl carbocation intermediates that undergo subsequent oxidation to the final products. Notably, the formation of acridone products involves an integrated oxidative dechlorination step.

Introduction

Nitrogen heterocycles play a pivotal role in drug discovery and pharmaceutical development, rendering their efficient synthesis and structural diversification a prominent area of research.[1] Among these, acridines, tricyclic N-heterocycles structurally related to anthracene, have progressed from their use as dyes and pigments[2] to contemporary relevance in medicinal chemistry. Their derivatives exhibit diverse biological activities, including antimalarial,[3] antibacterial,[4] antiviral,[5] anticancer,[6] and antileukemic[7] activities, as well as have the ability to inhibit the enzyme acetylcholinesterase.[8]

On the other hand, acridones, a subclass of acridines bearing a carbonyl group and a secondary amine at the C9- and C10-positions, respectively, have also garnered considerable attention. These scaffolds exhibit broad pharmaceutical relevance, with reported antiviral,[9] antimalarial,[10] and antibacterial[11] activities, and have been shown to act on multiple clinically validated targets in cancer therapeutics (Fig. 1).[12] In addition to their pharmacological significance, acridines and acridones also display noteworthy optical, photo-physical, and electrochemical properties, along with excellent photostability. These features make them attractive for a range of applications in materials science, including use as organic electronic devices,[13] organic light-emitting diodes (OLEDs),[14] and fluorescent probes for biomolecular imaging,[15] and in laser technologies.[16] Given their structural and functional versatility, the development of new synthetic approaches to access functionalized acridines and acridones remains highly desirable.

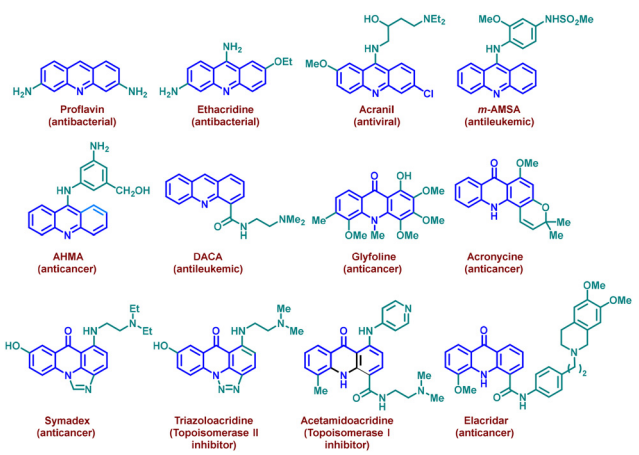

Fig. 1 Biologically active acridine/acridone derivatives.

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DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) is known as a powerful oxidant offering three accessible oxidation states, *i.e.*, oxidized quinone, one-electron reduced semiquinone, and two-electron reduced hydroquinone, that enables a wide array of oxidative transformations.[17] Because of this, DDQ has found broad utility in organic synthesis, particularly in the oxidation of alcohols,[18] phenols,[19] ketones,[20] aromatic compounds,[21] imines,[22] and heterocyclics.[23] It has also been employed in C–H bond functionalization,[24] C–C bond formation,[25] and dehydrogenation of saturated C–C,[26] C–O,[27] and C–N[28] bonds. Additionally, DDQ has demonstrated reactivity in cross-coupling reactions,[29] chlorination–oxidation tandem processes,[30] protecting group removal,[31] and even visible light-promoted reactions,[32] further underscoring its versatility. In tandem with advances in oxidative methodologies, several synthetic approaches toward acridine frameworks have been developed. For example, Nagarajan and co-workers developed a heteroannulation strategy with quinoline alkynyl aldehydes and indole for the synthesis of quino[2,3-*b*]carbazoles (Fig. 2A).[33] Later, Kim *et al.* disclosed a Rh(III)-catalysed C(sp^2)–H activation of benzaldehydes with anthranils followed by intramolecular electrophilic cyclisation, yielding 2-acyl acridines (Fig. 2B).[34] In a related strategy, the same group employed anthranils in a Rh(III)-catalysed C–H amination of aldimines, which similarly delivered 2-acyl acridine derivatives upon intramolecular cyclization (Fig. 2C).[35] In another approach, Balalaie *et al.* established a base-promoted formal [4 + 2]-cycloaddition reaction of allenoates and (*Z*)-2-(2-hydroxy-2-alkylvinyl)quinoline-3-carbaldehydes in the presence of Cs_2CO_3 for the synthesis of functionalized acridines under mild conditions through a sequential Michael addition, aldol condensation, and isomerisation process (Fig. 2D).[36] Recently, Langer *et al.* synthesised dibenzo[*a*,*j*]acridine and regioisomeric dibenzo[*c*,*h*]acridine derivatives by a combination of site-selective Pd-catalysed cross-coupling reaction and ring-closing alkyne–carbonyl metathesis (Fig. 2E).[37]

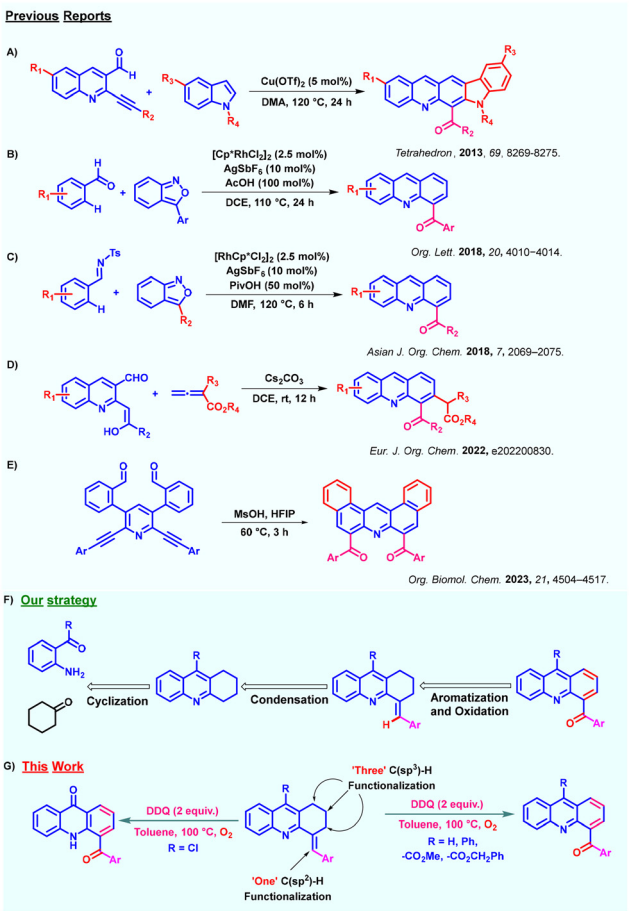

Fig. 2 Literature reports for the synthesis of acridin-4-yl(phenyl)methanone derivatives, our strategy and this work.

Considering the biological and materials relevance of acridines and acridones, efficient methods for their functionalization are highly desirable. Specifically, C4-acylated acridines (acridinyl ketones) represent valuable structural motifs. However, direct oxidative access to acridinyl ketones remains relatively underexplored, with current methods often relying on multistep synthetic sequences, the use of pre-functionalized substrates or transition-metal catalysis (as illustrated in Fig. 2). To address this synthetic deficiency and enhance step-economy, we envisioned a strategy that leverages oxidative cascade reactivity for the efficient construction of functionalized acridine frameworks (Fig. 2G). Building on our interest in acridine-based scaffolds,[38] and inspired by recent synthetic strategies, herein, we disclose a DDQ-mediated protocol that achieves aromatization-driven C(sp^2)–H oxidation across five contiguous carbon atoms of C4 functionalized 1,2,3,4-tetrahydroacridines, affording acridin-4-yl(aryl)methanones and 4-benzoylacridin-9(10*H*)-ones with broad functional group compatibility (Fig. 2G).

Towards this objective, we initiated our study by synthesising C4-functionalized 1,2,3,4-tetrahydroacridines (**3a–3u**) under deep eutectic solvent (DES) conditions (see the SI for details).[38*b*] Following this, compound **3a** was treated with DDQ (2 equiv.) in toluene (3 mL) at 80 °C to afford an acridine derivative. To our delight, these reaction conditions help dehydrogenative aromatisation and oxidation of vinylic C(sp^2)–H, leading to the formation of acridin-4-yl(phenyl)methanone (**4a**) in 30% yield (Table 1, entry 1). After confirmation of the product using complementary spectral data, we next focused on optimisation studies to improve the reaction yield. The investigated reaction conditions for the dehydrogenative oxidative functionalization of compound **3a** are summarised in Table 1. The solvent screening revealed that toluene was an effective solvent in comparison with other solvents screened for dehydrogenative aromatization and oxidation (Table 1, entries 1–7). Raising the reaction temperature from 80 °C to 100 °C led to a modest improvement in yield to 40% (Table 1, entry 8). However, increasing the DDQ loading from 2 equiv. to 4 or 6 equiv. did not result in any significant enhancement of the product yield (Table 1; entries 9 and 10). Gratifyingly, performing the reaction under a molecular O_2 atmosphere with 2 equiv. of DDQ in toluene at 100 °C afforded 2-acyl acridine

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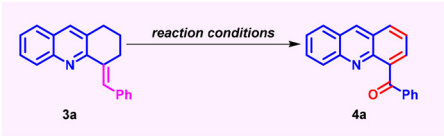
Table 1 Optimization of reaction conditions[a]

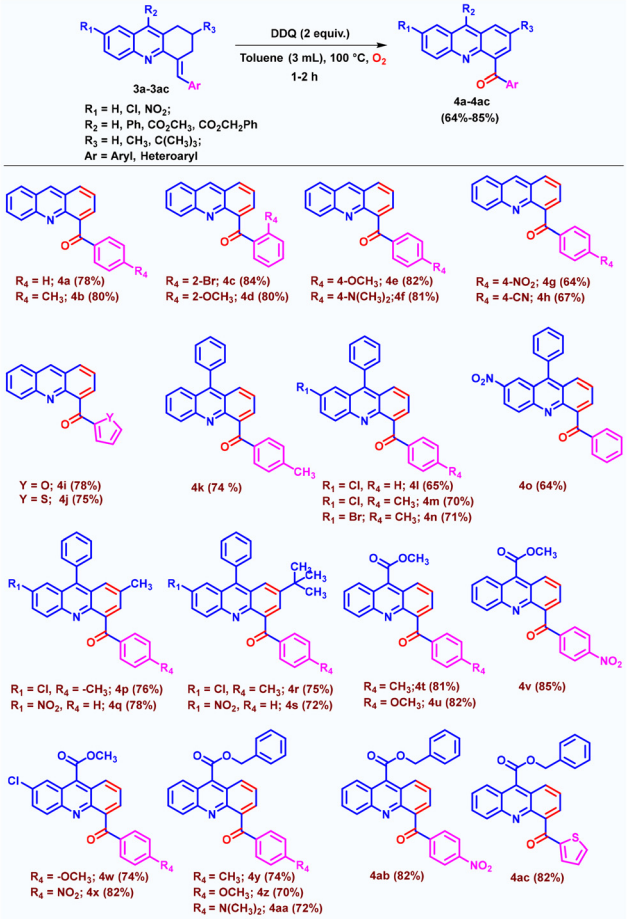


Sl. no.	Oxidant	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	DDQ	Toluene	80	6	30
2	DDQ	ACN	80	6	10
3	DDQ	DCE	80	6	20
4	DDQ	THF	80	6	Trace
5	DDQ	1,4-Dioxane	80	6	ND[c]
6	DDQ	DMSO	100	6	ND
7	DDQ	DMF	100	6	ND
8	DDQ[d]	Toluene	100	2	40
9	DDQ (4 equiv.)	Toluene	100	2	40
10	DDQ (6 equiv.)	Toluene	100	2	40
11	DDQ + O_2	Toluene	100	1	78[e] ± 2
12	DDQ + N_2	Toluene	100	2	Trace

[a] Reaction conditions: all the reactions were carried out with **3a** (0.5 mmol) and DDQ (2 equiv.) in 3 mL of toluene under a molecular O_2 atmosphere and conditions mentioned in the table. [b] Isolated yield. [c] Not detected. [d] Open air. [e] The isolated yield is the average of three runs (n = 3).

in 78% yield (Table 1; entry 11). The critical role of O_2 was validated by performing the reaction under air, which gave the desired product in 40% yield. Also, the same reaction was performed under a N_2 atmosphere to observe the formation of the desired product, but only a trace amount was formed (Table 1, entries 8 and 12). We also investigated the reaction in the presence of alternative oxidants/additives (TBN, $NaNO_2$, *m*-CPBA, TBHP, DMP, PIDA) in combination with DDQ, but these attempts failed to produce the desired product, resulting in complex mixtures (Table 1, entries 13–18in the SI). Among the conditions tested, 2 equiv. of DDQ under a molecular O_2 atmosphere in toluene at 100 °C (entry 11) were identified as the optimal conditions for this protocol.

With the optimized reaction conditions established, we proceeded to examine the scope and versatility of substrates for the developed dehydrogenative aromatization strategy (Scheme 1). This protocol exhibited robust performance across a wide range of C4-functionalized 1,2,3,4-tetrahydroacridines, affording acridin-4-yl(aryl)methanone derivatives (**4a–4ac**). The tolerance for diverse electronic and steric properties on the C4-aryl ring was first explored (**4a–4j**). The presence of *ortho* substituents (–Br, –OCH_3) was well tolerated, furnishing derivatives (**4c** and **4d**) in good yields, demonstrating the protocol's ability to handle steric hindrance. *para*-Substituted aryl rings bearing electron-donating (**4e** and **4f**) or heteroaryl (**4i** and **4j**) groups consistently provided good yields. Conversely, substrates with electron-withdrawing groups (**4g** and **4h**) afforded moderate yields. The protocol demonstrated robust efficacy with various substituents such as chlorine, bromine, and nitro at the C7-position (**4k–4o**) in good yields. Substitution with alkyl groups such as –CH_3 and –$C(CH_3)_3$ at the C2-position



Scheme 1 Substrate scope of acridin-4-yl(aryl)methanone derivatives. Unless otherwise mentioned, all the reactions were conducted using **3** (0.5 mmol) and DDQ (2 equiv.) in 3 mL of toluene at 100 °C under a molecular O_2 atmosphere for 1–2 h. The yields are calculated based on the isolated quantities of the product.

proceeded smoothly, providing the corresponding acridinyl ketones (**4p–4s**) in moderate to good yields. Before the aforementioned positions, the protocol also demonstrated compatibility with other key functional groups. Notably, the incorporation of ester functionalities at the C9 position resulted in excellent yields, particularly when a *para*-nitro group was present on the appended aryl ring. This performance significantly surpassed the yields obtained with analogous methyl and methoxy substituents (**4t**, **4u**, **4w**, **4y–4aa**). A similar high efficiency was observed with the ester at the C9-position, where *para*-nitro substitution on the aryl ring consistently afforded the aromatized–oxidised products in very good yields (**4v**, **4x**, **4ab**). A heterocyclic thiophene unit was also compatible, providing an 82% yield (**4ac**). These collective findings underscore the broad applicability and robustness of our developed methodology for synthesizing a diverse array of substituted acridine derivatives.

Surprisingly, subjecting 4-benzylidene-9-chloro-1,2,3,4-tetrahydroacridine (**6a**) to dehydrogenative aromatization with DDQ resulted in an oxidative dechlorination, affording 4-benzoyla-

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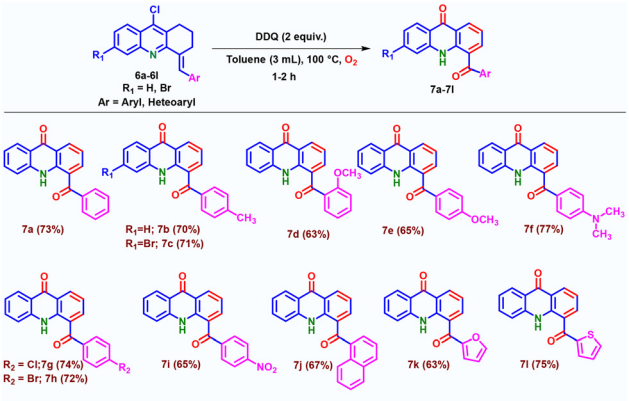
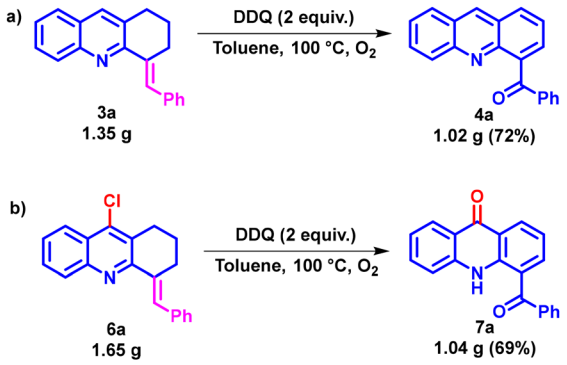


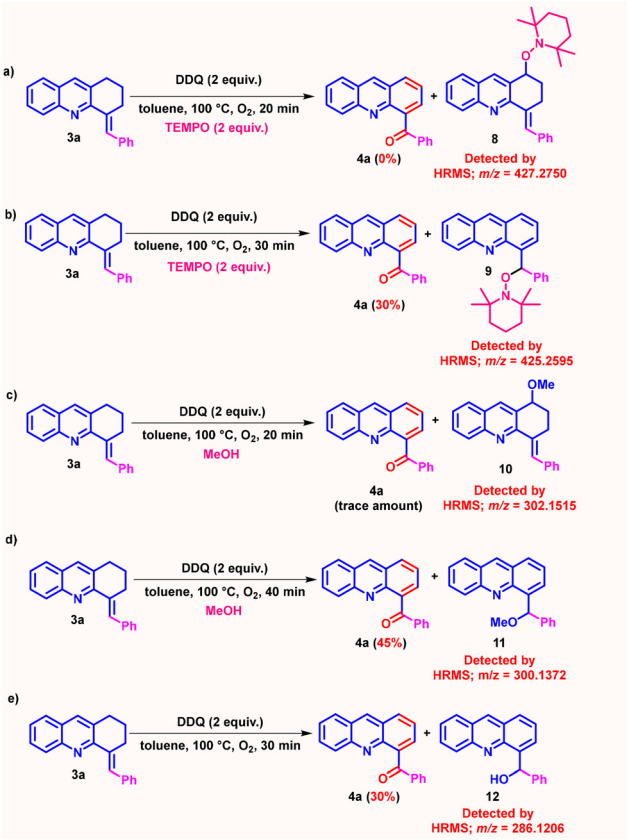
Scheme 2 Dehydrogenative aromatisation for the synthesis of 4-benzoylacridin-9(10*H*)-one derivatives. Unless otherwise mentioned, all the reactions were conducted with **6** (0.5 mmol) and DDQ (2 equiv.) in 3 mL of toluene at 100 °C under a molecular O_2 atmosphere for 1–2 h. The yields are calculated based on the isolated quantities of the products.

cridin-9(10*H*)-ones (**7a–7l**) in good yields (Scheme 2). The structures of the products were confirmed by spectral analysis (^{1}H, ^{13}C, and LC-HRMS). In this case too, the substrate scope was studied by varying the substitution on the 4-arylidene-9-chloro-1,2,3,4-tetrahydroacridine derivatives for dehydrogenative aromatisation using DDQ. As a general trend, the nature of the substituents at the C4-position had minimal influence on the aromatization process, with the reaction proceeding efficiently for a diverse array of functional groups, including both aromatic and heteroaromatic substituents. For example, substrates bearing electron-donating groups such as $-CH_3$, $-OCH_3$, and $-N(CH_3)_2$ were readily converted to the aromatized products (**7b–7f**) in good yields. Halogen-substituted aryl groups such as chloro and bromo were also well tolerated, providing the desired products (**7g** and **7h**) in 74% and 72% yields, respectively. A moderate decrease in yield (65%) was observed for the nitro-substituted derivative (**7i**), likely due to its strong electron-withdrawing nature. Furthermore, naphthalene, furan, and thiophene derivatives (**7j**, **7k**, and **7l**) underwent effective transformation under the oxidative conditions, affording yields ranging from 63% to 75%. This substrate scope highlights the broad applicability of this protocol for synthesizing structurally diverse benzoylacridin-9(10*H*)-ones. To show the scalability of this metal-free protocol, the synthesis of product **4a** or **7a** was successfully carried out on a gram-scale. Starting with 1.35 g (5.0 mmol) of the C4-functionalized tetrahydroacridine (**3a**), the optimized DDQ-mediated oxidation furnished the acridine-4-yl(aryl)methanone (**4a**) product in 72% (1.02 g) yield (Scheme 3). The more complex cascade synthesis of the acridone scaffold also demonstrated robustness. 1.65 g (5.0 mmol) of the 9-chloro derivative (**6a**) was smoothly converted to afford **7a** in a good 69% isolated yield (1.04 g).

To gain mechanistic insights into the DDQ-mediated dehydrogenative aromatisation, a series of control experiments were carried out. As shown in Scheme 4, each sub-experiment



Scheme 3 Gram-scale synthesis of **4a** and **7a**.



Scheme 4 Control experiments to establish the reaction mechanism.

was designed to probe a specific mechanistic stage in the DDQ-mediated oxidation sequence. The reaction was first performed in the presence of TEMPO, a well-known radical scavenger. The formation of the corresponding TEMPO-adduct (**8**), confirmed by HRMS (Scheme 4a), supports the involvement of radical intermediates in the reaction pathway. In a parallel experiment, **3a** when treated with DDQ followed by the addition of TEMPO after 15 min of starting the reaction yielded a TEMPO-adduct (**9**) (confirmed by HRMS; Scheme 4b), indicating the existence of the radical nature of

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the pathway and reaction sequence, *i.e.* aromatisation and C(sp^2)–H oxidation. To further examine the mechanistic sequence, **3a** was reacted with DDQ in the presence of MeOH as a nucleophile to observe the formation of **4a**. It is noteworthy that the HRMS analysis after 20 minutes indicated the presence of a MeOH adduct (**10**), revealing the formation of a carbocation (Scheme 4c). The same was analysed (HRMS analysis) after 40 min to observe the formation of a methoxy adduct (**11**) (Scheme 4d). This indicates that the reaction proceeds *via* aromatization followed by C(sp^2)–H oxidation. This was further supported by the detection of a hydroxylated intermediate (**12**) for subsequent oxidation of the C-OH group to furnish the final ketone (**4a**) (Scheme 4e). Taken together, these observations clarify the stepwise transformation from tetrahydroacridine to acylated acridine, highlighting the radical-to-cationic mechanism operating in this cascade.

In light of the aforementioned mechanistic investigation and literature reports,[17,23,39] a plausible mechanism for the present DDQ-mediated dehydrogenative aromatisation and C(sp^2)–H oxidation of 1,2,3,4-tetrahydroacridines is proposed, as depicted in Fig. 3. A hydrogen atom transfer (HAT) from 1,2,3,4-tetrahydroacridines to DDQ followed by single electron transfer (SET) along route A instead of *via* route B (SET and then HAT) is presumed to be the predominant pathway for the formation of a resonance-stabilised benzyl carbocation (**II** or **II′**). Subsequently, the carbocation (**II** or **II′**) undergoes DDQH-assisted H-elimination to furnish the dihydroacridine species (**III** or **III′**). These intermediates then participate in a HAT process to generate radical **IV** or **IV′**, which undergoes tautomerization to form a more stabilized radical species (**V** or **V′**). A subsequent SET process takes place to deliver the acridinyl carbocation (**VI** or **VI′**), while suppressing another competitive pathway involving the initial SET, followed by HAT. Finally, nucleophilic attack by the H_2O molecule on **VI** or **VI′**, followed by the DDQ-mediated dehydrogenation closing cycle, delivers the corresponding product **4** or **VIII′**.

In the case of 9-chloro-1,2,3,4-tetrahydroacridine derivatives, the initially formed (aromatised and C(sp^2)–H oxidised) intermediate (**VIII′**) further undergoes dechlorination *via* the formation of carbocation intermediate **IX′**. Then the nucleophilic attack by the H_2O molecule provides a hydroxylated ketone (**XI′**), which upon tautomerisation yields the final com-

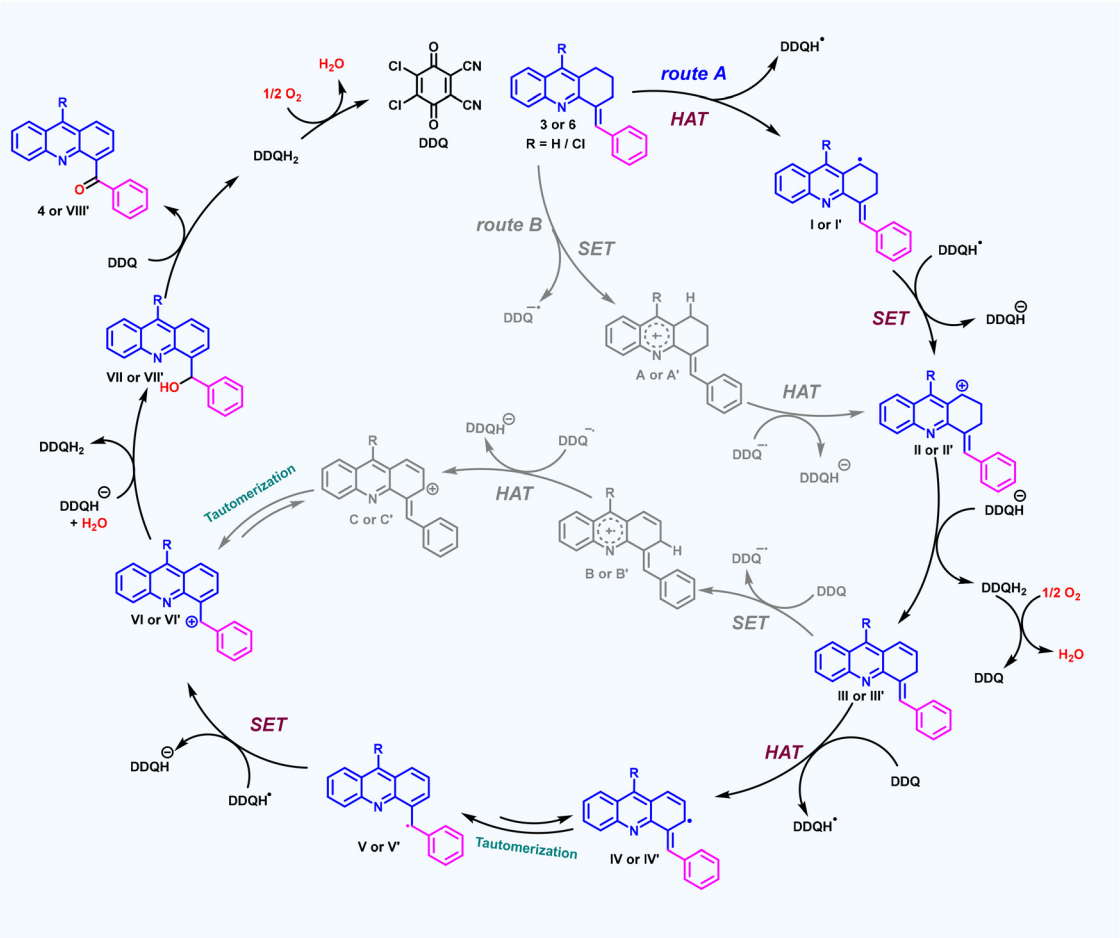

Fig. 3 Plausible mechanism for the DDQ-mediated dehydrogenative aromatisation and C(sp^2)–H oxidation of C4-functionalized 1,2,3,4-tetrahydroacridines.

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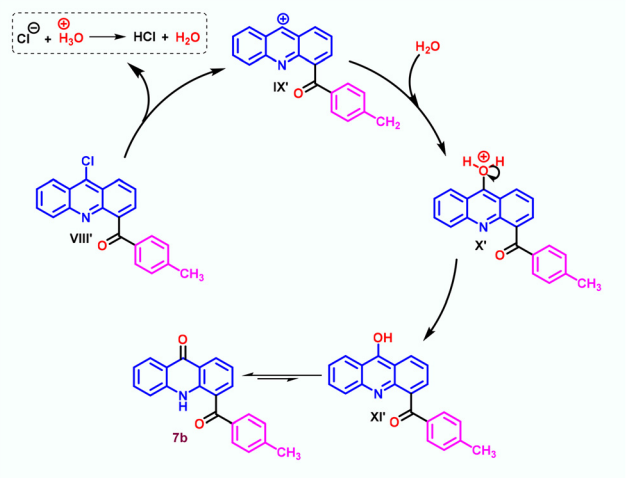

Fig. 4 Plausible mechanism for the dechlorination of (9-chloroacridin-4-yl)(phenyl)methanone.

pound 7 (Fig. 4). To confirm the elimination of Cl^-, a control experiment was performed where the gas effluent was introduced into a solution of silver nitrate ($AgNO_3$) to give a white precipitate (AgCl) (for more details see the SI), indicating the release of chloride ions (Cl^-) from the C9 position into the reaction medium.

Conclusions

In conclusion, we have developed a DDQ-mediated oxidative cascade protocol for the synthesis of acridin-4-yl(aryl)methanones and 4-benzoylacridin-9(10*H*)-ones *via* dehydrogenative aromatisation and C(sp^2)–H oxidation of C4-functionalized 1,2,3,4-tetrahydroacridines. This metal-free transformation proceeds under mild reaction conditions, exhibits a broad substrate scope, and demonstrates tolerance to diverse functional groups, affording the desired products in good yields. The operational simplicity and versatility of this method highlight its potential utility for accessing diverse acridine-based scaffolds of interest in both medicinal chemistry and materials science.

Author contributions

T. Shirisha and D. Kashinath designed the work, and S. Majhi and A. Parida performed all the synthesis and characterization studies. T. Shirisha and A. Parida contributed to the synthesis of the starting materials. The manuscript was written by T. Shirisha, S. Majhi and D. Kashinath. All authors have approved the final version of the article before submission.

Conflicts of interest

There are no conflicts to declare.

Data availability

The analytical data of the compounds reported in this article are available in the article and its supplementary information (SI). ^{1}H-NMR, ^{13}C-NMR and High Resolution Mass data of all newly synthesized compounds are given in the supplimentary information. See DOI: https://doi.org/10.1039/d5ob01306b.

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