Synthesis of Acridinium Photocatalysts via Site-Selective C–H Alkylation

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Acridinium dyes have been broadly used as photocatalysts, but it remains synthetically challenging to fine-tune their catalytic performance by functionalization of their structural cores. Acridinium photocatalysts are usually prepared through de novo synthesis, which involves difficult steps and requires sensitive organometallic reagents. Herein, we report a modular and scalable synthesis of acridinium photocatalysts with diversely functionalized core structures through site-selective late-stage C(aryl)-H alkylation. The alkylation is achieved by inducing cross-coupling between acridinium salts and organotrifluoroborates with visible light, followed by electrocatalytic dehydrogenation. The late-stage diversification is compatible with organotrifluoroborates bearing a broad array of electronically and sterically diverse substituents, allowing rapid and convenient access to a library of 3,6-functionalized acridinium photocatalysts with novel photocatalytic properties. A four-step continuous-flow reactor system was also developed to achieve 3,6-dialkylation of acridinium dyes without need for intermediate manipulation.

Keywords: acridinium photocatalysts, electrocatalysis, photocatalysis, C–H alkylation, flow chemistry

Introduction

Over the last decade, advances in photoredox catalysis have significantly altered the landscape of organic synthesis by allowing a wide variety of synthetic transformations to proceed efficiently under extremely mild conditions.¹–⁷ While these photochemical transformations predominantly employ transition-metal complexes based on ruthenium and iridium as catalysts,¹ organic photocatalysts offer increased sustainability and potentially unique reactivities.² One class of organic photocatalysts that has gained popularity is acridinium dyes, which were pioneered by Fukuzumi et al.⁸ and characterized by their high excited-state reduction potentials. Unfortunately, bleaching of the Fukuzumi catalyst 1 has been reported in many applications and been ascribed to side reactions between nucleophiles and the Me group or acridinium core.⁹,¹⁰ Nicewicz et al.¹¹ have reported a more robust acridinium photocatalyst 2 (Figure 1a), in which the nitrogen was substituted with a phenyl ring and the 3,6-positions with two tert-butyl groups. Importantly, the same research group has very
recently revealed that acridine radical $2^\cdot$ also allows access to strong reducing power under photoirradiation.\cite{12} Given the synthetic versatility of 2 in many challenging chemical transformations,$^{13-15}$ modification of its acridinium core with other substituents can provide a viable strategy to fine-tune the catalytic performance of acridinium dyes. This concept, despite its great potential, has remained largely unexplored likely due to the challenges synthesizing functionalized acridinium dyes.

Acridinium dyes are commonly prepared by adding an aryl Grignard reagent to an acridone and then treating the resultant reaction mixture with an acid (Figure 1b, top left).\cite{16} Unfortunately, functionalized acridones can be challenging to synthesize,$^{11}$ which has prompted researchers to explore new synthetic routes to acridiniums. DiRocco et al.$^{17}$ and Sparr et al.$^{18-20}$ have reported the preparation of methoxy- or amino-substituted acridinium salts through Friedel-Crafts reaction of a symmetric triarylamine derivative with 2,4,6-trimethylbenzoyl chloride (Figure 1b, bottom left) or the addition of a 1,5-dimetallic dianilide to an aryl ester (Figure 1b, bottom right). Recently, Nicewicz et al.$^{21}$ have improved the synthesis of 3,6-di-tert-butyl-substituted acridinium dyes, for which the reaction of a doubly lithiated biaryl ether with an ester served as the key step (Figure 1b, top right). While these methods provided access to a broad range of acridinium dyes substituted on the nitrogen atom or at the 9-position, it remains challenging to

Figure 1 | Synthesis of acridinium photocatalysts. (a) Representative acridinium photocatalysts. (b) Previous work: synthesis through de novo construction of the acridinium core. (c) This work: synthesis through modular, site-selective late-stage C–H alkylation.

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functionalize the acridinium core with satisfactory chemo- and regioselectivity.

In contrast to the aforementioned approaches that rely on de novo synthesis, we envision the construction of decorated acridinium photocatalysts via C–H functionalization of existing acridinium dyes. Photochemically induced single-electron transfer (SET) between acridiniums and organotrifluoroborates is known to generate a persistent acridine radical and a transient alkyl radical, which we hypothesize could be coupled to form a C–C bond in the absence of radical acceptors. Herein, we report the synthesis of acridinium photocatalysts via site-selective late-stage C–H alkylation using organotrifluoroborates through sequential photochemical addition and electrocatalytic dehydrogenation (Figure 1c). This modular method shows excellent scalability and functional group compatibility, allowing rapid access to a broad array of novel acridinium dyes with diverse substituents at the 3,6-positions that are difficult to synthesize with existing methods. A four-step continuous-flow synthesis has also been developed to achieve 3,6-dialkylation without the need for intermediate manipulation.

Results and Discussion

First, we explored the monoalkylation of commercially available acridinium salt 1 with various organotrifluoroborates through a one-pot, two-step process consisting of sequential processes of photochemical addition and electrocatalytic dehydrogenation (Figure 2). As a start, the addition of organotrifluoroborate to 1 was induced by 0.5 h of blue LED irradiation (see Supporting Information Figure S1 for details of setup), followed by the addition of...
2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as the redox catalyst and KPF₆ as the supporting electrolyte. Electrolysis of the resultant reaction mixture at a constant current of 10 mA afforded the desired 3-alkylated acridinium product in good to excellent yields (73–97%) without the detection of any other regioisomers. Note that electrolysis in the absence of TEMPO resulted in sluggish conversion. This method demonstrated excellent compatibility with primary (3–10), secondary (11–18), and tertiary (19–22) alkylorgano-trifluoroborates, providing easy access to acridinium dyes with different steric properties. The mild reaction conditions also enabled the introduction of chemically labile functional groups that have been found to be difficult to generate via previously reported methods, such as phthalimides (10), ketones (16 and 17), and esters (22). 4-Alkyl-1,4-dihydropyridines can also serve as alkylation reagents, as demonstrated in the synthesis of 14.

A highly useful feature of our method is that the monoalkylated product can be alkylated again following the steps (1) and (2).

Figure 3: Scope of dialkylation of acridinium dyes. Reactions were conducted at 0.3 mmol scale. See Supporting Information Table S3 for crystal data of 31. *Irradiation for 2.5 h. ^A 1,4-dihydropyridine-based acyl donor was employed.
above experimental procedures to generate novel, 3,6-
dialkylated acridinium dyes, using the same (28–45) or a
different (23–27, 46) organotrifluoroborate donor (Figure 3). Replacing the 9-Mes group with a 2,6-dimethyl
substituent, or the N-methyl to an N-benzyl or N-aryl moiety, did not affect the C–H alkylation reactions. The
low yields for 28, 29, and 32 were caused by the reduced efficiency for the second alkylation. Preinstalled 2,7-F
(43), Me (44), or OMe (45) groups hampered the introduction of ‘Bu, but not ‘Pr groups, at positions 3 and 6,
implying the importance of steric hindrance as a determining factor. Finally, in addition to alkylation, acylation
was also possible by employing a 1,4-dihydropyridine-based acyl donor,46 as demonstrated with the synthesis
of an asymmetrically-substituted acridinium 46.

The alkylation reaction could be scaled up to decagram without difficulty by employing a continuous-flow photochemical reactor45,46 and an electrochemical batch reactor, as demonstrated in the synthesis of 10.88 g of 36 in 80%
yield (Figure 4a). The combination of multiple reactors into a single, continuous-flow sequence has been an increasing popullar practice in organic synthesis due to improved efficiency and elimination of the need to isolate the intermediates.47,48 However, the integration of both photochemical and electrochemical flow reactors49–51 into multistep continuous-flow platforms remains unexplored.52 Building upon our previous experience in flow electrosynthesis,53–55 we achieved four-step continuous-flow synthesis of 35 using a reaction system that consisted of two photochemical and two electrochemical flow reactors (Figure 4b). Briefly, a solution of compound 1 and ‘Bu-BF₃K (1.5 equiv) was pumped through a photochemical reactor and then mixed with a solution of TEMPO and Et₃N before entering a flow electrolysis cell. Unlike batch electrolysis, Et₃N was necessary to improve the conversion of electrocatalytic dehydrogenation in flow. However, bases are detrimental to the photochemical step and were neutralized before the

**Figure 4** | Gram-scale synthesis. (a) Decagram synthesis of photocatalyst 36 employing a continuous-flow photochemical reactor and an electrochemical batch reactor (see Supporting Information Figure S2 for details). CH₂CN/H₂O (5:1) was employed as the solvent. (b) Four-step continuous-flow synthesis of photocatalyst 35 (see Supporting Information Figure S3 for details). CH₂CN/H₂O (5:1) was employed as the solvent except that TEMPO and Et₃N were dissolved in CH₂CN/CH₂COCH₃/H₂O (5:6:1).

**Figure 5** | Photocatalytic decarboxylative conjugate addition. Acridinium dyes were evaluated with 4CzIPN and an Ir-based catalyst, which are known to induce photochemical decarboxylation.

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reaction mixture entered the second photoreactor. The efflux from the first electrolytic reactor was received with a flask to remove H₂ bubbles before being pumped out to sequentially mix with TFOH to neutralize Et₃N and then with tBu-BF₃K. The resultant mixture subsequently went through a second set of photoreactor and electrolytic cell, with the same TEMPO and Et₃N treatment in between, to afford 1.40 g (51% yield) of the dialkylated product 35.

Overall, the platform provides on-demand production of 3,6-disubstituted acridinium photocatalysts. Electrochemical examination of the 3,6-disubstituted acridinium dyes showed that they could all be reduced into the corresponding neutral acridine radicals in a reversible manner. However, the reduction of acridinium employed for the synthesis 45 appeared irreversible, showing the importance of the iPr groups at the 3 and 6 positions in stabilizing the reduced acridine radical. The fluorescence lifetimes of the acridinium dye products synthesized in our study varied from a few nanoseconds to over 30 ns, with 42 (τ = 30.7 ns) exhibiting the longest lifetime ever reported for acridinium salts (Supporting Information Table S1). These results clearly demonstrated that the fluorescence lifetime was tunable via modulation of the substituents on the acridinium core.

The acridinium dyes were then applied as photocatalysts to the redox-neutral decarboxylative conjugate addition of 48 to an electron-deficient alkene 49 (Figure 5; and Supporting Information Table S2). Notably, 30, 35, and 45 outperformed well-established photocatalysts such as acridinium 1 and 36, 4CzIPN, and [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆.

Investigation of the reaction intermediates in the photochemical coupling of acridinium 47 with tBu-BF₃K revealed the formation of 3,4-dihydroacridinium 51 following neutral aqueous workup, or 3,10-dihydroacridine 53 if NaOH was added after the irradiation (Figure 6a). Repeating the reaction in deuterated solvents indicated that one of the protons at the 4-position of 51 originated from H₂O. Based on these results, a plausible mechanism for the C–H alkylation of acridinium dyes was proposed (Figure 6b). SET oxidation of tBu-BF₃K by excited acridinium 47 affords a transient radical tBu⁺ and a persistent acridine radical I, both of which undergo cross-coupling to furnish 3,10-dihydroacridine 53. Alternatively, tBu⁺ can

**Figure 6** | Mechanistic experiments and proposal. (a) Photochemical reaction of 47 with tBu-BF₃K. (b) Proposed mechanism for the C–H alkylation of acridinium dyes. (c) An alternative mechanism for the formation of 51.
add to the inherently reactive 3-position of 47 to generate a radical cation II, which then reacts with I via SET to furnish 53 and concomitantly regenerate 47 (Figure 6c). Protonation of 53 affords 3,4-dihydroacridinium 51, which is no longer reactive due to its smaller conjugation system and does not undergo further alkylation. Meanwhile, 51 is much more difficult to oxidize ($E_{1/2} = 2.10 \text{ V vs SCE}$) than 53 ($E_{1/2} = 0.27 \text{ V vs SCE}$), and can revert to the latter via deprotonation by OH$, which is generated by cathodic reduction of solvent H2O. In the electrocatalytic step, TEMPO-mediated oxidation of 53 leads to the formation of alkylated acridinium product 54. Computed singly occupied molecular orbital (SOMO) of 1 revealed positions 1, 3, 6, and 8 to exhibit much greater unpaired electron densities than 2, 4, 5, and 7 (Figure 6b). Positions 1 and 8 are much more sterically hindered than positions 3 and 6, explaining the site selectivity for the alkylation reactions at positions 3 and 6.

Conclusions

We have developed a practical method to synthesize various 3,6-functionalized acridinium photocatalysts through site-selective late-stage C-H alkylation. These reactions can be performed under mild conditions and display broad functional group compatibility as well as excellent scalability. Our synthetic approach allows us to easily fine-tune the photocatalytic properties of acridinium dyes by chemically modifying their cores with an array of electronically and sterically diverse substituents. Catalytic applications of the newly obtained acridinium dyes in a benchmark reaction reveal the benefits of the structural variation in enhancing photocatalytic efficiencies.

Supporting Information

Supporting Information is available and includes experimental procedures, spectral characterization, cyclic voltammograms, crystal data, and additional data. Crystal structure data of compound 31 (CCDC: 1965076) have been deposited in the Cambridge Structural Database.

Conflict of Interest

There is no conflict of interest to report.

Acknowledgments

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