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Micellar Catalysis: Visible-light mediated imidazo[1,2-a]pyridine C-H amination with *N*-aminopyridinium salt accelerated by surfactant in water

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Keywords

Visible-light | Water | Micellar catalysis | *N*-aminopyridinium salt | Imidazo[1,2-a]pyridine

Main observation and conclusion

A light-promoted metal-free protocol for the amination of imidazo[1,2-a]pyridines with *N*-aminopyridinium salt by the assistance of surfactants in water was reported, charactering mild and environmentally benign conditions, as well as great functional group tolerance. Micelles with negative charge polar surface and hydrophobic core formed from sodium dodecyl sulfate serve as an ideal medium for visible-light mediated radical reaction of cationic pyridine salt and midazo[1,2-a]pyridine in aqueous phase. The electrostatic interaction between positively charged of *N*-aminopyridinium and negatively charged on the micelles is of great significance in this method.

Comprehensive Graphic Content

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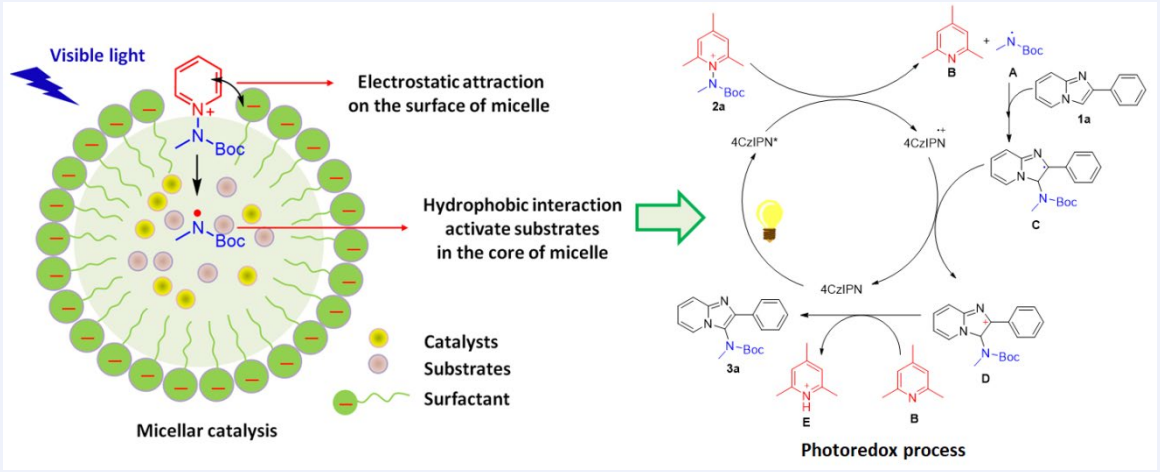


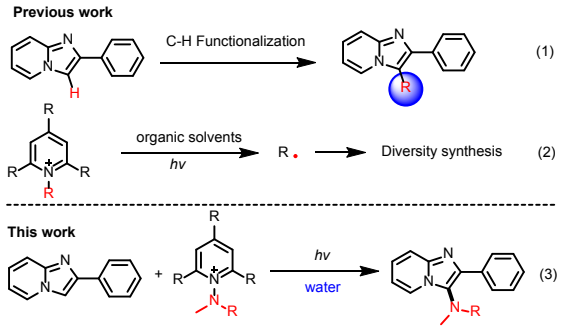
Background and Originality Content

As a high-frequent and key structural motify in *N*-heteroarenes, imidazo[1,2-a]pyridine has extensively existed in many pharmaceutical, such as zolpidem, zolimidine, olprinone, saripidem, alpidem, and minodronic acid, etc,[1] showing anticancer, anti-inflammatory, antiviral, and other biological activities.[2] Due to the importance of this promising scaffold, great achievements for the building of various functionalized imidazo[1,2-a]pyridines have been made in recent years (Scheme 1, (1)).[1a, 2a-c, 3] However, the amination of imidazo[1,2-a]pyridines is rare.[3g, 3i-k, 3m, 3p] Despite these achievements, developing methodologies with mild and sustainable conditions using new *N*-radical for the selective C–H functionalization of imidazo[1,2-a]pyridines is still highly desired.

In the meantime, as a novel radical precursor, pyridinium salt has been widely used for regioselective functionalization of substituted arenes and heteroarenes for the past few years (Scheme 1, (2)).[4] Significantly, *N*-aminopyridinium salts were used for introduce amino groups for compounds under the irradiation of visible-light.[5] However, all of these reactions in relate to aminopyridinium salts were conducted only in organic phase, and there was no one reported in green solvent water.

Though water as a solvent bears many merits, such as being safe, nontoxic, environmentally benign, and inexpensive, etc, but the big problem is the insolubilization of substrates and catalysts.[6] Our laboratory's long-term enrichment of the water phase reaction experience shows that the matter of mass transfer from insoluble substrates and catalyst in water can be settled by introducing amphiphilic surfactant into water to form aggregates as micro reactors.[7]

Scheme 1 Selective C–H functionalization of imidazo[1,2-a]pyridines



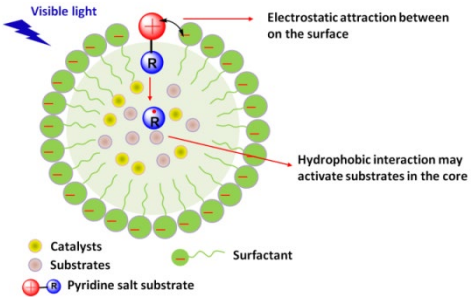
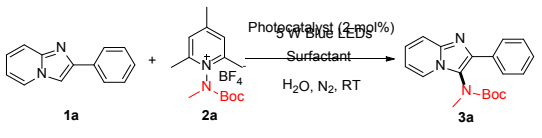


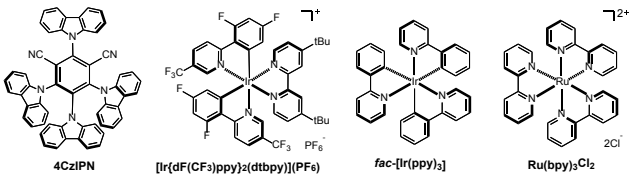
Figure 1 Micellar free radical reactions involving ionic substrates

Studies have shown that micelles formed by self-assembly of ionic surfactants with polar hydrophilic surfaces and hydrophobic cores can be used as an ideal media for visible light reactions.[6e, 6f, 7a, 8] In the hydrophilic area of micelles, the charged surface can adsorb ionic substrates with opposite charges, and the hydrophobic core can dissolve fat-soluble catalysts and substrates, which greatly increase both the ionic and hydrophobic compounds in micelles. What's more, the micelle effect may activate the substrates, especially the hydrophobic interaction.[7c, 7d] Thus, with these effects in micelle, the reaction between ionic and hydrophobic substrates could be processed well in water under visible-light conditions (Figure 1). Hence, a green protocol that combines visible-light as energy and water as a solvent to realize C-H amination of imidazole compounds has been proposed (Scheme 1, (3)), accomplishing the reaction between the polar cationic *N*-aminopyridinium salts amino radical precursor and nonpolar imidazo[1,2-a]pyridines in water for the first time.

Results and Discussion

Table 1 Optimization of the reaction conditions[a]





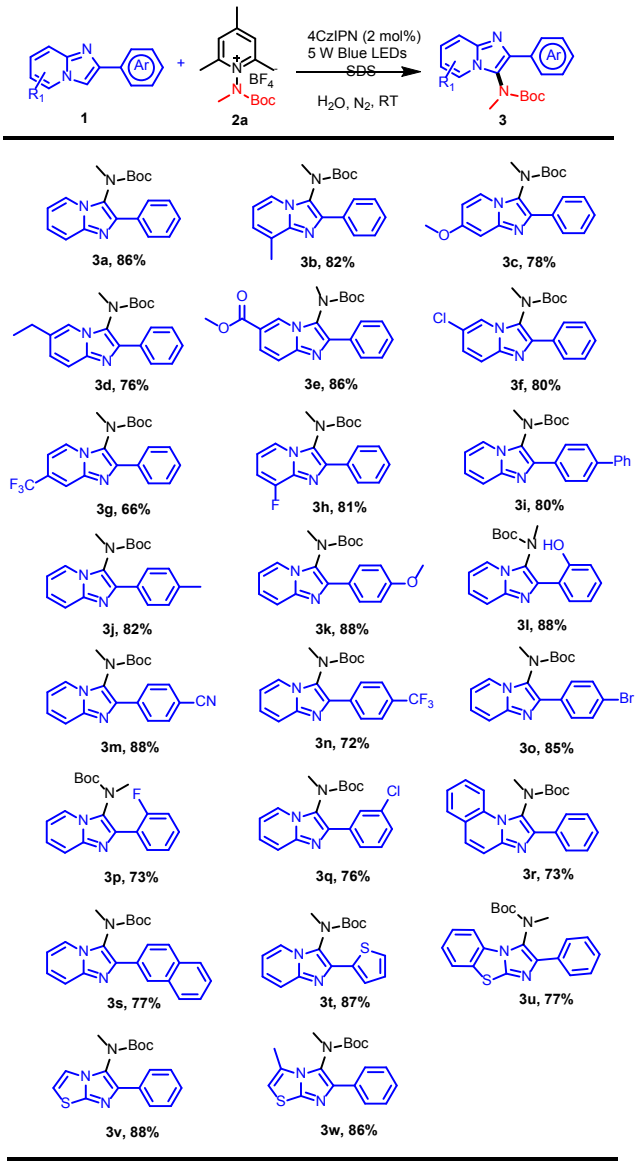
Entry	Photocatalyst	Surfactant (equiv)	Yield (%)[b]
1	$Ir(ppy)_3$	SDS	72
2	$(Ir[dF(CF_3)ppy]_2$	SDS	66

	(dtbpy))PF_6		
3	$Ru(bpy)_3Cl_2$	SDS	Trace
4	4CzIPN	SDS	86
5	4CzIPN	SDBS	72
6	4CzIPN	Sodium laurylsulfonate	56
7	4CzIPN	Bromohexadecyl pyridine	NR
8	4CzIPN	Dihexadecyldime-thylammonium bromide	NR
9	4CzIPN	CTAB	NR
10	4CzIPN	Tween 80	32
11	4CzIPN	Polyoxyethylene lauryl ether	36
12	4CzIPN	None	trace
13	None	SDS	trace
14[c]	4CzIPN	SDS	NR
15[d]	4CzIPN	SDS	trace
16	4CzIPN	SDS(0.25)	66
17	4CzIPN	SDS(0.5)	48

[a] Reaction conditions (unless otherwise stated): 0.2 mmol of **1a**, 1.2 eq of **2a**, 2 mol% of photocatalyst, 0.15 eq surfactant in water 4 mL, 5 W Blue LEDs, at N_2 atmosphere and room temperature reaction for 24 h; NR = No reaction; CTAB = Cetyltrimethylammonium bromide; SDS = Sodium dodecyl sulfate; SDBS = Sodium dodecylbenzene sulfonate. [b] Isolated yield. [c] Without light. [d] At air atmosphere.

To test our hypothesis, we initiated our exploration by employing 2-phenylimidazo[1,2-a]pyridine **1a** and *N*-aminopyridinium **2a** as the model substrates under the atmosphere of N_2 and the irradiation of 5 W blue LEDs at room temperature (Table 1). Firstly, several photocatalysts including 4CzIPN, $Ir(ppy)_3$, $Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$, and $Ru(bpy)_3Cl_2$ were explored in the presence of SDS (entries 1–4). We were pleased to find that 4CzIPN was the best photocatalyst, delivering the desired product **3a** in excellent isolated yield (86%, entry 4). Then, several surfactants including both nonionic and ionic surfactants were screened (entries 4-11). All the anionic surfactants have achieved good results (entries 4-6), and the SDS gave the best results (entriy 4). It is worth noting that cationic surfactants worked poorly due to the electrostatic repulsion between positive charge surface and *N*-aminopyridinium salt (entries 7-9), which lowered the concentration of substrates **2a** in micelles. Lower yield was given when nonionic surfactants were used (entries 10, 11). The yield was not increased when the concentration of SDS was up to 0.25 or 0.5 eq (entries 16-17). Expectedly, desired product was not given in the absence of photocatalyst, surfactant, light, or N_2 (entries 12-15).

Table 2 Scope of imidazo[1,2-a]pyridine[a, b]

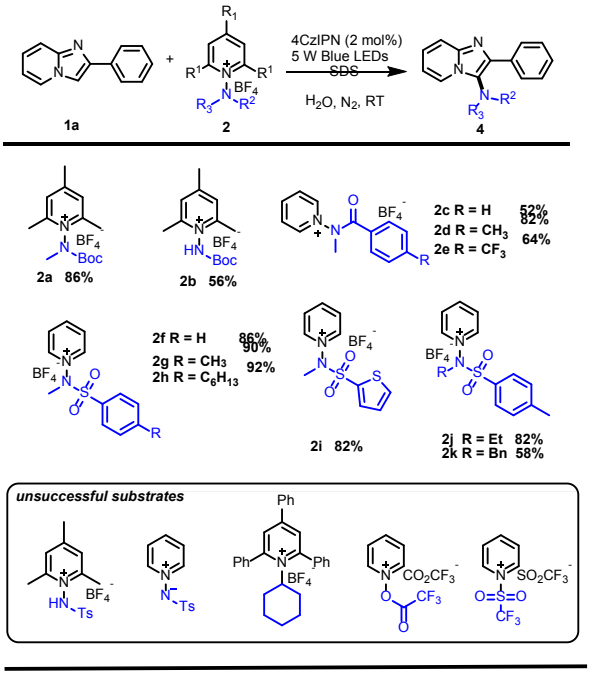


[a] Reaction conditions (unless otherwise stated): 0.2 mmol of **1**, 1.2 eq of **2a**, 2 mol% of 4CzIPN, 0.15 eq SDS in water 4 mL, 5 W Blue LEDs, at N_2 atmosphere and room temperature reaction for 24 h. [b] Isolated yield.

With optimized conditions in hand, we next explored the substrate scope of this protocol. As shown in Table 2, substituents **1** ($-CH_3$, $-OMe$, $-CH_2CH_3$, $-COOCH_3$ $-F$, $-Cl$, $-CF_3$) on the pyridyl ring could proceeded smoothly with *N*-aminopyridinium **2a**, leading to the target products **3a**–**3h** in moderate to good yields (66%–86%). Furthermore, 2-aryl imidazo[1,2a]pyridines **1** bearing electron-donating groups ($-CH_3$, $-OMe$, $-OH$) or electron-withdrawing groups ($-CN$, $-CF_3$, $-Br$, $-F$, $-Cl$) all reacted smoothly to give the target amination imidazo[1,2-a]pyridines **3i**–**3q** with good yields

(72–88%) in phenyl moiety. It should be noted that imidazo[1,2-a]pyridines substituted by heterocyclic groups could still proceed well with the optimized conditions (**3r**-**3t**). To our delight, the corresponding thiomethylated products (**3u-3w**) could be obtained in satisfactory yields.

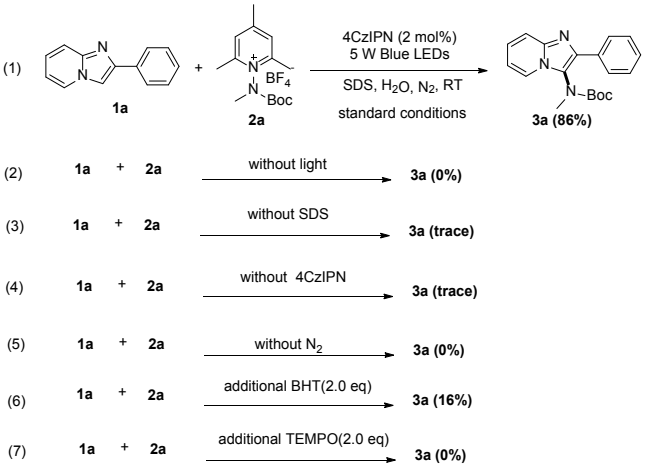
Table 3 Scope of *N*-aminopyridinium salt.[a, b]



[a] Reaction conditions (unless otherwise stated): 0.2 mmol of **1a**, 1.2 eq of **2**, 2 mol% of 4CzIPN, 0.15 eq SDS in water 4 mL, 5 W Blue LEDs, under N_2 atmosphere and room temperature reaction for 24 h. [b] Isolated yield.

Next, we commenced exploring the scope of pyridinium salts **2**. As it is seen in Table 3, the amidyl radicals ($RSO_2N•R^1$, RCON•Me, tBuOCON•H) stemmed from the corresponding *N*-aminopyridinium salts involved in the amination to give the desired imidazo[1,2-a]pyridines (**2a**-**2k**) in moderate to excellent yields. Interestingly, compared with pyridinium salts **2a**, the substrate **2b** without methyl substitution gave a lower yield, indicating that the methyl substitution on nitrogen may have the function of stabilizing *N*-radicals. It is worth mentioning that there are some pyridinium salts showing no activity with this method, as shown in Table 3.

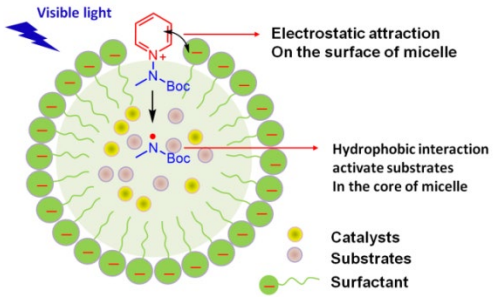
Scheme 2 Mechanism study.



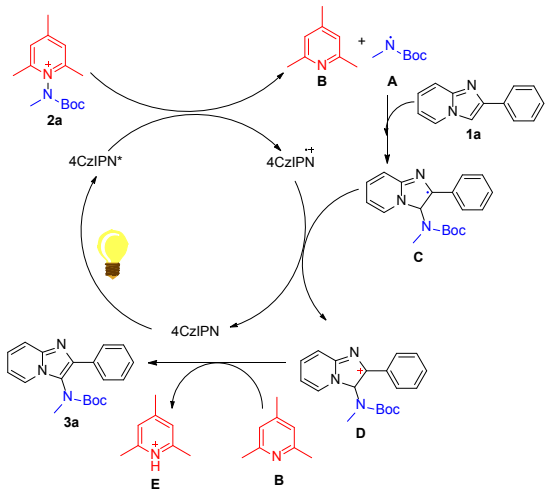
In order to explore the mechanism of the reaction, several control experiments were accomplished (Scheme 2). The results of (1) and (3) indicated that micellar catalysis was involved. These results showed that photocatalyst (4), surfactant (3), light (2), and N_2 (5) were the necessary conditions. Moreover, this transformation could be terminated completely by introducing TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) (7), suggesting the reaction was proceeded via radical pathway. And also the addition of BHT (butylated hydroxytoluene) gave rise to a sharp decrease of the yield (16%) (6).

Based on the above investigations and previous reports,[3a, 4, 7a, 7d] a possible mechanism was provided (Figure 2). As shown in Figure 2a, as an excellent precursor of *N*-radical, water-soluble *N*-aminopyridinium salt with cationic polar structure could be embedded on the polar surface of micelles with negative charge due to electrostatic attraction, which greatly increased the concentration of pyridinium salt in micelles. Simultaneously, the concentration of all nonpolar reactants, including imidazo[1,2-a]pyridine and photocatalyst, in the hydrophobic core of micelles significantly increased due to the hydrophobic interaction in the core of micelle.

Thus, with this micelle effect, *N*-radical could be generated easily under the visible-light irradiation in water, followed by a photoredox process in micelle to finish the follow-up reaction. The Figure 2b showed the detailed process. Firstly, 4CzIPN is excited by blue light to form 4CzIPN*. Pyridinium salt **2a** is reduced by excited species 4CzIPN*, giving *N*-radical **A** and pyridine **B**. Then, *N*-radical **A** selectively attacks imidazo[1,2-a]pyridine to afford radical **C**. After SET oxidation of **C**, cationic species **D** was given, followed by deprotonating to yield the final product **3a**.



(a) Micellar catalysis



(b) Photoredox process

Figure 2 Proposed mechanism.

Conclusions

In conclusion, we have firstly reported a versatile and environmentally benign stragety for the amination of diverse imidazo[1,2-a]pyridines by employing *N*-aminopyridinium salt as radical precursors in aqueous, which accelerated by anion surfactant. Micelles formed from amphiphilic anion surfactant SDS not only increased the concentration of polar cation *N*-aminopyridinium salt on the negative charge surface of micelle, but also the lipid-soluble imidazo[1,2-a]pyridine and photocatalyst in the hydrophobic core of micelles, which effectively addressed the mass transfer problem in water and promoted the reaction greatly. The using of water as a solvent and visible-light as energy source to develop a more environmentally friendly synthesis method for amino-imidazo[1,2-a]pyridines shows significant research value.

Experimental

In a reaction tube equipped with a magnetic stir bar was charged with 40 mg (0.20 mmol) of 2-phenylimidazo[1,2-a]pyridine **1a**, 83.5 mg (0.24 mmol) of *N*-aminopyridinium **2a**, 9.2 mg of sodium dodecyl sulfate (SDS) and 3.2 mg (2 mol %) 4CzIPN were added in 4 mL of water at room temperature, N_2 atmosphere, under irradiation with 5W blue LED for 24 h. After completion of the reaction, the mixture was extracted with EtOAc and dried over anhydrous Na_2SO_4, after removal of EtOAc under vacuum, crude mixture left out was purified by column chromatography (silica gel 300-400 mesh size) using petroleum ether and ethyl acetate, the product **3a** was isolated.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

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Micellar Catalysis: Visible-light mediated imidazo[1,2-a]pyridine C-H amination with *N*-aminopyridinium salt accelerated by surfactant in water

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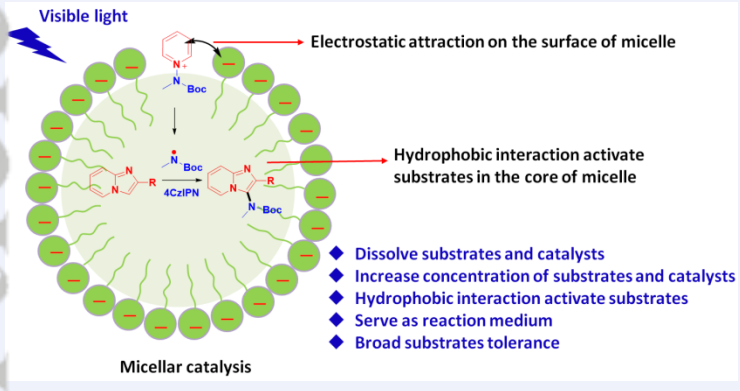

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