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Visible light induced oxidative coupling of purines with arenes

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ABSTRACT

The photocatalyzed synthesis of 9-arylpurines has been developed using 9*H*-purines and non-activated arenes. This method is highly atom economical using an acridinium photocatalyst induced by visible light under air atmosphere at room temperature. It employs no metal or external oxidant for the synthesis of 9-arylpurine derivatives.

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Purines are important structural motifs in biological and pharmaceutical chemistry because of their antivirus and antitumor activities [1–6]. Purine derivatives with the aryl group on the N9 position (Fig. 1) are potential anxiolytic and antidepressant agents [7–10], potential antituberculosis drugs [11] and enterovirus inhibitors [12]. Thus, the development of green and novel synthetic methodologies for the straightforward construction of structurally diverse 9-arylpurines is currently of great importance in the pharmaceutical chemistry.

Traditionally, there are three general routes for the direct N9-arylation of purines using activated arenes *via* a C–N cross-coupling reaction (Scheme 1). Arylboronic acids, diaryliodonium salts and aryl halides were used to achieve the arylation of various purine derivatives [13–15]. In 2003, Bakkestuen and Gundersen developed a regioselective purine N9-arylation reaction under mild conditions employing arylboronic acid in the presence of $Cu(OAc)_2$ and phenanthroline (Phen) (Scheme 1a) [16]. In 2011, Niu and co-workers reported an efficient and novel protocol of copper-catalyzed arylation using diaryliodonium salts as the aryl source (Scheme 1b) [17]. After that, Larsen and Ulven described a CuBr and 4,7-bis(2-hydroxyethylamino)-1,10-phenanthroline (BHPhen) co-catalyzed arylation approach of purine skeletons with aryl halides (Scheme 1c) [18]. Despite these distinguished advances, some of these synthetic strategies suffer from certain limitations such as long reaction times, high reaction temperatures and/or harsh reaction conditions. Consequently, the development of an eco-friendly and novel synthetic protocol for the preparation of structurally diverse 9-arylpurine derivatives using simple arylation reagents is highly desirable.

The recent development of visible light photocatalysis provides a mild and powerful tool for organic synthesis [19–24]. Romero and co-workers introduced aromatic $C(sp^2)$–H amination *via* an acridinium photoredox catalyst with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a co-catalyst [25]. Later, Niu and co-workers reported an oxidant-free strategy for $C(sp^2)$–N bond formation using a dual catalytic system combining an acridinium photooxidant with a cobalt complex [26]. Herein, we report a simple and mild metal-free 9-arylpurine synthesis *via* $C(sp^2)$–H activation of the arene induced by visible light using air as the oxidant (Scheme 1d).

Initially, we optimized the conditions using 6-chloropurine (**1a**) and mesitylene (**2a**) as model substrates, and the results are summarized in Table 1. At first, we chose commercially available organic dyes for the desired transformation. Using methylene blue or Eosin Y did not provide the desired product (Table 1, entries 1 and 2). Gratifyingly, the use of 9-mesityl-10-methylacridinium perchlorate (Acr^+–Mes ClO_4^-) gave the desired product **3a** in 92% yield (Table 1, entry 3). 9-Mesityl-10-phenylacridinium tetrafluoroborate (Mes–Acr^+–Ph BF_4^-) was also tried, but it was less effective (Table 1, entry 4). Different commonly used photocatalysts were then screened (Table 1, entries 5–7). To our delight, we found that 2,4,6-triphenylpyrylium tetrafluoroborate (TPT) was an effi-

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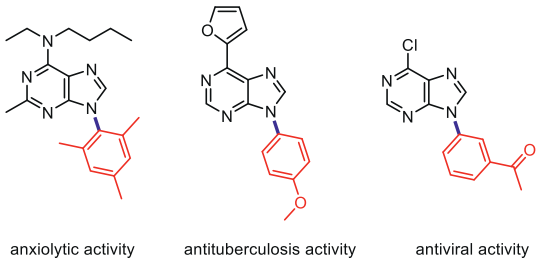
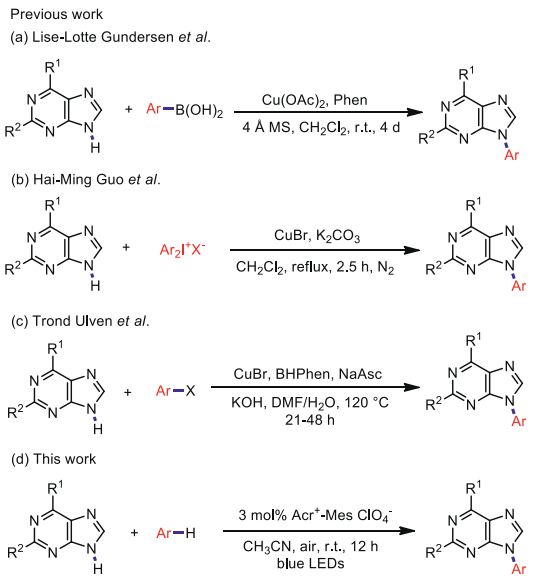
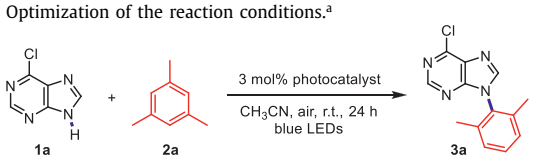


Fig. 1. Examples of 9-arylpurines with biological activities.



Scheme 1. Synthesis routes of 9-arylpurines.

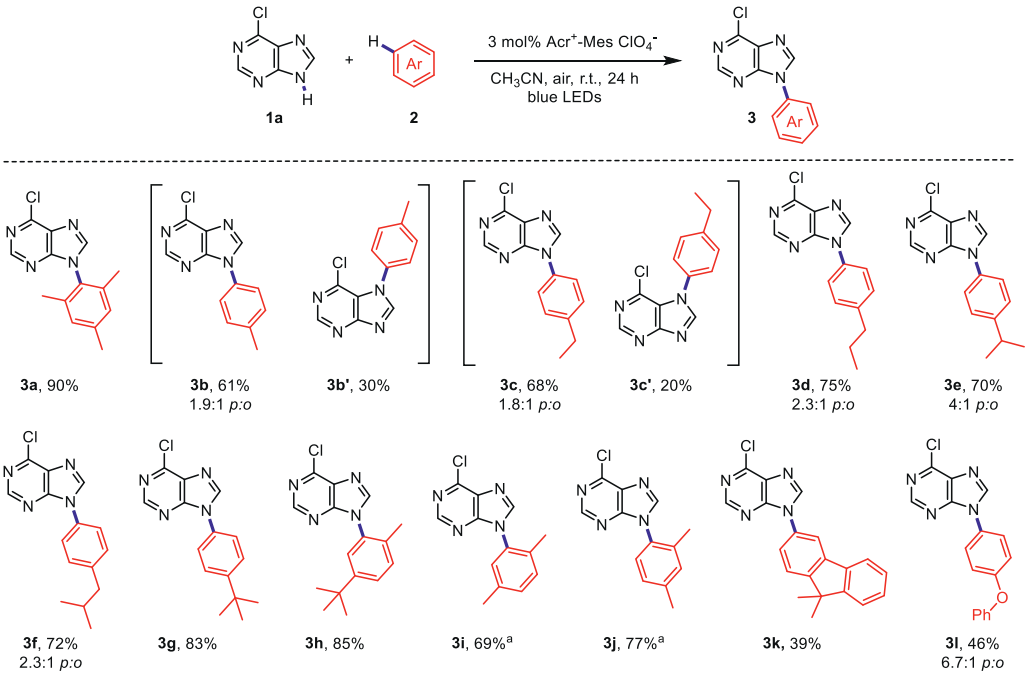
Table 1
Optimization of the reaction conditions.[a]



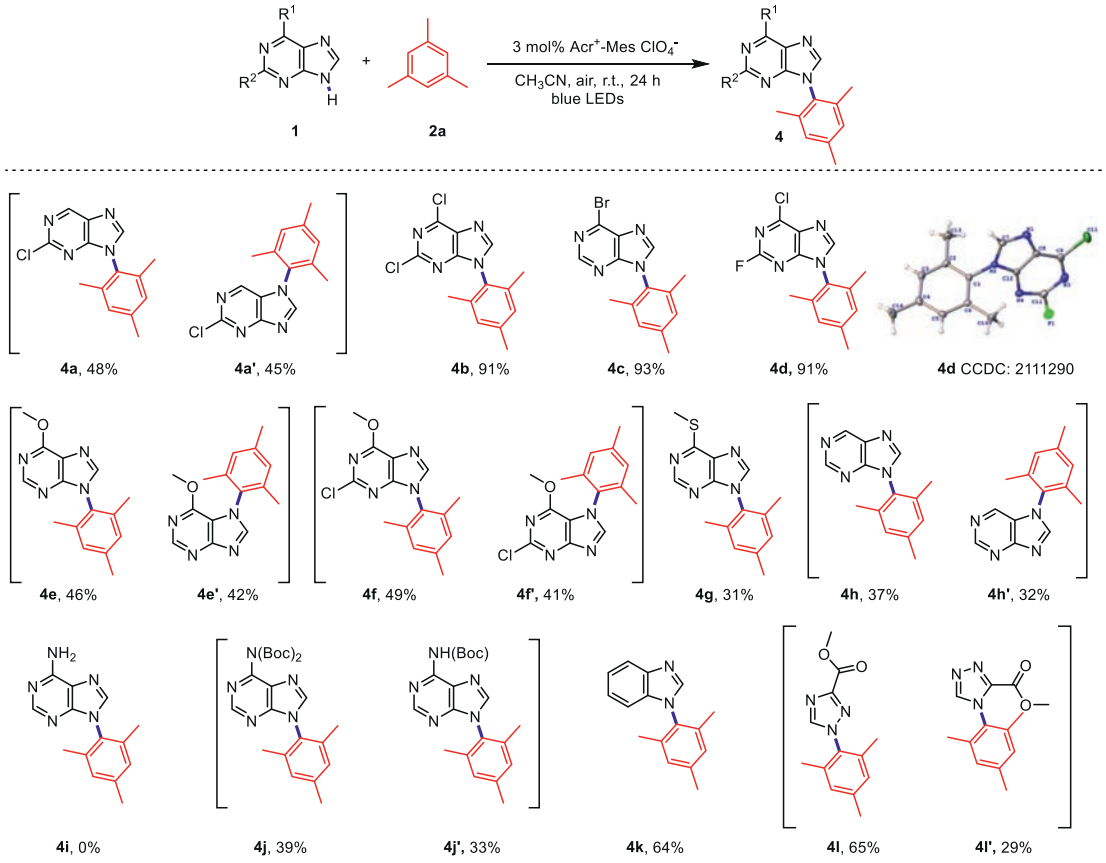
Entry	Photocatalyst	Solvent	Yield (%)[b]
1	Methylene blue	CH_3CN	N.D.[c]
2	Eosin Y	CH_3CN	N.D.
3	Acr^+–Mes ClO_4^-	CH_3CN	92
4	Mes–Acr^+–Ph BF_4^-	CH_3CN	43
5	$Ru(bpy)_3Cl_2$	CH_3CN	N.D.
6	$Ir[dF(Me)ppy]_2(dtbbpy)PF_6$	CH_3CN	N.D.
7	TPT	CH_3CN	92
8	Acr^+–Mes ClO_4^-	DCM	10
9	Acr^+–Mes ClO_4^-	1,2-DCE	59
10	Acr^+–Mes ClO_4^-	CH_3OH	55
11	Acr^+–Mes ClO_4^-	THF	65
12	Acr^+–Mes ClO_4^-	DMSO	N.D.
13	Acr^+–Mes ClO_4^-	DMF	N.D.
14	Acr^+–Mes ClO_4^-	DMA	N.D.
15[d]	Acr^+–Mes ClO_4^-	CH_3CN	82
16[e]	Acr^+–Mes ClO_4^-	CH_3CN	90
17[f]	Acr^+–Mes ClO_4^-	CH_3CN	N.D.
18	–	CH_3CN	N.D.
19[g]	Acr^+–Mes ClO_4^-	CH_3CN	N.D.

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.4 mmol), photocatalyst (3 mol%) in CH_3CN (2.0 mL) under air, irradiated by 3 W blue LEDs at room temperature for 24 h.
[b] Determined by GC using dodecane as an internal standard.
[c] N.D = not detected.
[d] Acr^+–Mes ClO_4^- (1 mol%).
[e] Acr^+–Mes ClO_4^- (5 mol%).
[f] Under an Ar atmosphere.
[g] Reaction performed in the dark.

cient photocatalyst providing our C–N coupled product **3a** in 92% yield as well. However, because of the relatively low stability of TPT [27,28], we chose Acr^+–Mes ClO_4^- as the photocatalyst. The subsequent screening of various solvents indicated that this reaction was not effective in polar aprotic solvents (entries 12–14). In-



Scheme 2. Substrate scope of arenes. Reaction conditions: **1** (0.1 mmol), **2** (0.4 mmol), Acr^+–Mes ClO_4^- (3 mol%) in CH_3CN (2.0 mL) under air atmosphere, irradiated by 3 W blue LEDs at room temperature for 24 h. The ratio of the isomer was determined by nuclear magnetic resonance. Isolated yields are shown. [a] Arenes **2** (1.0 mL) were used.

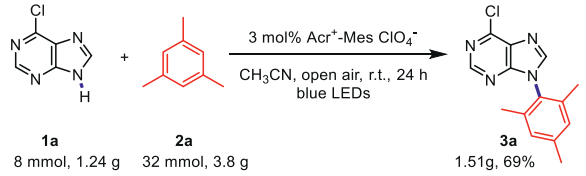


Scheme 3. Substrate scope of purines. Reaction conditions: **1** (0.1 mmol), **2** (0.4 mmol), Acr^{+}–Mes ClO_4^{-} (3 mol%) in CH_3CN (2.0 mL) under air atmosphere, irradiated by 3 W blue LEDs at room temperature for 24 h. The ratio of the isomer was determined by nuclear magnetic resonance. Isolated yields are shown.

creasing or decreasing the catalyst amount was not beneficial (entries 15 and 16). Furthermore, in the absence of air, no target product was detected (entry 17). Additionally, the control experiments indicated that the photocatalyst and visible light are indispensable for this transformation (Table 1, entries 18 and 19). In the end, the optimal reaction results were obtained using 3 mol% of Acr^{+}–Mes ClO_4^{-} in 2 mL CH_3CN, under air, at room temperature, and with blue light irradiation (Table 1, entry 3).

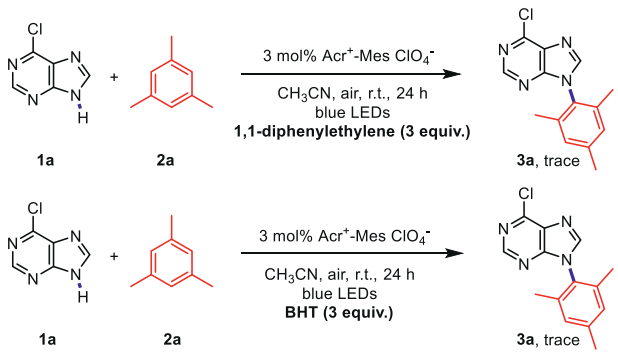
After getting the optimized reaction conditions, the scope of this C–N cross-coupling reaction was investigated by reacting 6-chloropurine (**1a**) with a variety of arenes. As shown in Scheme 2, many arenes were suitable for this transformation (**3a**–**3j**). This reaction occurred mainly on the N9 position of the purines, but also on N7 position, like **3b** and **3b'**, **3c** and **3c'**. With other substates like **3d–3l**, only a trace amount of N7-aryl products were produced. Because of the steric hindrance between chlorine on N6 position and the methyl group on mesitylene, we only get N9-substituted product **3a**. Delightfully, 9,9-dimethyl-9*H*-fluorene and diphenyl oxide were reactive (**3k**, **3l**). In addition, halo, nitro or amino substituents on the phenyl ring were not tolerated under the reaction conditions.

Next, the coupling of mesitylene with a series of purine derivatives under the optimized conditions was carried out (Scheme 3). With halo substituents on the purine ring, the target compound was produced in ≥90% yields (**4b–4d**). In addition, the structure of **4d** was certified by single-crystal X-ray diffraction analysis. The electron-donating groups were also well tolerated (**4e**, **4f**). Unsubstituted purine afforded a separable regioisomeric mixture with a total yield of 69% (**4h**). Unfortunately, adenine did not provide the desired product in this catalytic system (**4i**). It is worth mentioning that when protected adenine **3j** was used, one Boc group was probably lost during the reaction to provide both **4j** and **4j'** with a total yield of 72%. To our delight, benzimidazole and methyl 1,2,4-triazole-3-carboxylate were also efficiently *N*-arylated (**4k**, **4l**).

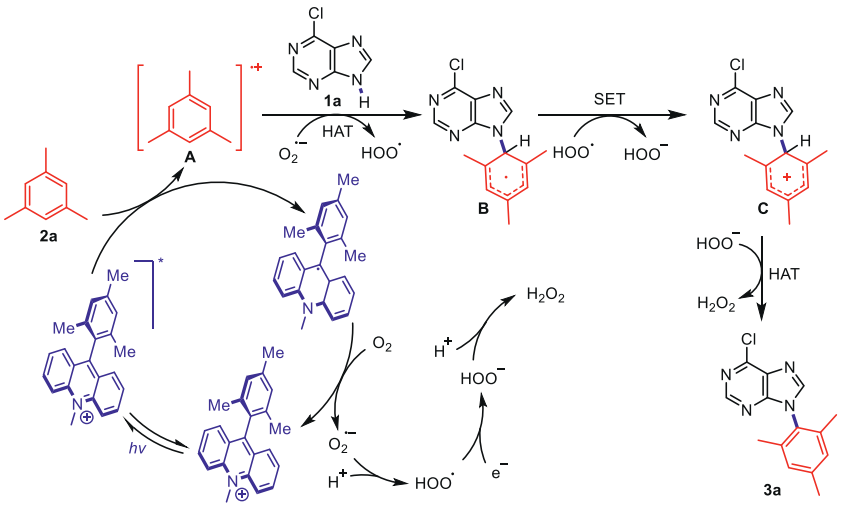


Scheme 4. Gram-scale experiment.

In addition, we conducted a gram-scale experiment to demonstrate the utility of this method (Scheme 4). The expected product was formed in 69% yield under the optimized conditions, demonstrating the procedure's potential application in industrial processes.



Scheme 5. Radical trapping experiment.



Scheme 6. Proposed reaction mechanism.

In order to gain more insight into the reaction mechanism, a few control experiments were carried out (Scheme 5). When radical scavengers like 1,1-diphenylethylene or 2,6-di-*tert*-butyl-4-methyl phenol (BHT) were added, only a trace amount of product was detected by GC-MS, which indicates that a radical pathway might be involved.

Based on the above results and previous reports [25,26,29–32], a plausible mechanism is proposed (Scheme 6). The photocatalyst $Acr^+–Mes\ ClO_4^-$ is excited by blue LEDs to generate its excited state $[Acr^+–Mes\ ClO_4^-]^*$, which then undergoes a single electron transfer (SET) process with mesitylene **2a** to generate mesitylene radical cation **A** and Acr–Mes radical, which is oxidized by O_2 to generate superoxide $O_2^{\bullet-}$ and complete the photocatalyst cycle. Then, $O_2^{\bullet-}$ undergoes a hydrogen atom transfer (HAT) with **A** and **1a** to form intermediate **B** and HOO•. Subsequently, **B** is oxidized by HOO• to form **C** *via* an SET pathway. Finally, deprotonation of **C** produces the desired product **3a**, along with the formation of H_2O_2, which was detected by a starch-iodide experiment (see Supporting information for details) [29,33]. Furthermore, fluorescence quenching study and cyclic voltammetry experiments (see Supporting information for details) support an SET process [34] between the excited state $[Acr^+–Mes\ ClO_4^-]^*$ and mesitylene.

In conclusion, we have reported a highly atom economical method for the synthesis of 9-aryl purine derivatives. Using an acridinium photooxidant under blue light irradiation, arene radical cations are generated and form $C(sp^2)$–N bond with the N9–H in purines. Additionally, other nitrogen heterocycles, benzimidazole and methyl 1,2,4-triazole-3-carboxylate, were also used as the nitrogen source. These compounds are important structural motifs in biological and pharmaceutical fields. Compared with previous methods, this metal-free and external oxidant-free purine N9-arylation protocol which occurs under ambient atmosphere while at room temperature, is more attractive and more eco-friendly.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2022.04.065.

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