Visible Light-Induced EDA-Mediated C-3 Coupling of Quinoxalin-2(1*H*)-ones with Unactivated Aryl Iodides

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ABSTRACT: -

Visible light-induced C-3 arylation of quinoxalin-2(1*H*)-ones with abundantly available aryl iodides with good yields *via* an EDA-complex formation has been accomplished. Both aryl/heteroaryl iodides and quinoxalin-2(1*H*)-ones possessing electron-donating as well as electron-withdrawing groups were coupled well to access the desired products in good yields. The radical scavenging, EPR, UV-visible experiments, and quantum yield revealed that the reaction went through a radical pathway *via* a SET process. Furthermore, the protocol could also be applied for the synthesis of biologically active molecules, illustrated the practicability of the present protocol.

Introduction: -

In the past decades, C-3 functionalization of quinoxalin-2(1*H*)-ones has gained significant attention as several useful methodologies such as arylation,[1] alkylation,[2] amination,[3] acylation,[4] and sulfenylation,[5] are being developed. Amongst these, C-3 arylation of quinoxalin-2(1*H*)-ones has emerged as a hot topic owing to immense biological activities of the product molecules in medicinal chemistry (**Figure 1**).[6,7]

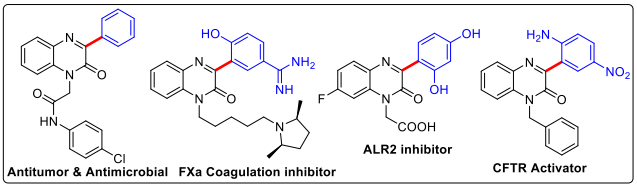


Figure 1 Biologically active C-3 arylated quinoxalin-2(1*H*)-ones moieties.

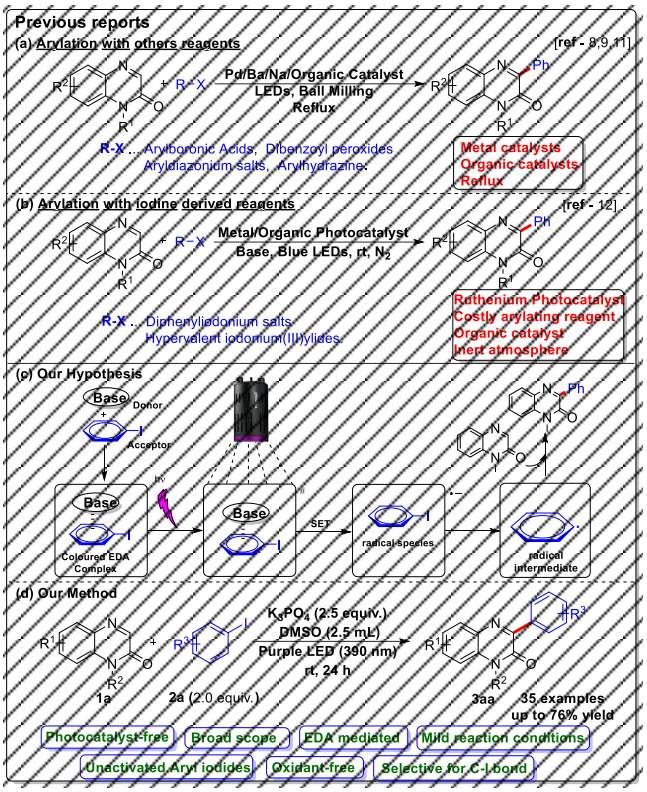
Traditionally, synthesis of C-3 arylated quinoxalin-2(1*H*)-ones relied on transition-metal-assisted cross- or oxidative coupling strategies utilizing expensive metals, ligands, and oxidants under harsh reaction conditions with limited substrate scope.[8] In addition, mechano- and electro-triggered C-3 arylation of quinoxalin-2(1*H*)-ones have flaws like usage of aryl diazonium salts (stability issues) and employment of expensive piezo-electric materials and electrolytes.[9]

In the last decade or more, photoredox-catalysis has emerged as one of the most important tools in organic synthetic chemistry owing to its sustainability and eco-friendly nature.[10] In this context, various C-3 aryl radical precursors have been recently emanated for the arylation of quinoxalin-2(1*H*)-ones under visible light phtoredox catalysis.[11] In one set of reaction, the authors have explored aryl hydrazine and aryl acyl peroxides on substrates under oxidative coupling conditions. However, the use of these substrates raises alarming safety and handling issues both during preparation and use in the reaction (**Scheme 1a**). In the second set of reaction[12] by Zhang, Murarka, Wu and co- workers have generated aryl radical from diaryl iodonium salts, and hypervalent iodine(III) ylides under visible light photoredox catalysis. However, these strategies suffered from several issues, like employment of photocatalysts and by-products formation, which have poor E-factor, atom economy, and multiple-step synthesis. **Scheme 1b**).

For a majority of hypervalent iodine compounds, aryl iodides are the precursor and therefore, direct use of aryl iodides as aryl radical precursors can be extremely prudent and save environmentally taxing derivatizations. Direct use of aryl iodides in such transformations can be a game changer owing to its accessibility, stability, and cheapness. However, the imminent problem with the use of aryl iodides as aryl radical precursors under visible light photoredox conditions is its high redox potential[13] (−2.2 V/SCE and BDE ~65 kcal mol^{-1}) which is a major deterrent for its incompatibility with a majority of photoredox catalysts used in this domain.

In the last few years, electron-donor-acceptor (**EDA**) based photoinduced transformations have garnered a significant traction as a tool to counterweight redox potential mismatch of participating substrates.[14] In the above

context, we hypothesized that if a suitable EDA-complex may be formed between an electron donor (base) and aryl iodides, a SET may lead to the generation of the aryl radical irrespective of the high redox potential of aryl iodides **(Scheme 1c).**



Scheme 1. Previous reports and present methodology for C-3 arylation of Quinoxalin-2(1*H*)-ones**.**

In this context, based on previous reports, and in continuation to our EDA-mediated strategies,[15] we, herein, demonstrate the first example of C-3 arylation of quinoxalin-2(1*H*)-ones using aryl iodides as aryl radical precursors under photocatalyst-free conditions. (**Scheme 1d**).

Results and discussion: -

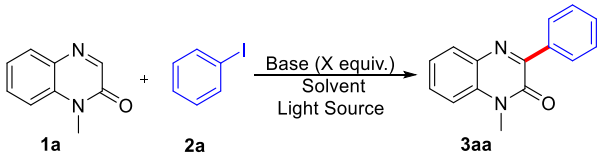
Initially, we started with *N*-methylquinoxalin-2(1*H*)-one (**1a**, 0.25 mmol) and phenyl iodide (**2a**, 0.50 mmol) as model substrates to optimize the reaction conditions using Cs_2CO_3 (0.50 mmol) under the illumination of purple LED as shown in **Table 1**. Pleasantly, we obtained the C-3 arylated quinoxalin-2(1*H*)-one, **3aa**, in moderate 51% yield (entry 1, **table 1**). In order to improve the yield, we first investigated a range of bases such as K_3PO_4, NEt_3, $NaHCO_3$, Na_2CO_3, and K_2CO_3, revealing that K_3PO_4 was more efficacious (**details in SI, table S2**). Later, the employment of various solvents (DMSO, DMA, DMF, ACN and DCE etc.) in a series of reactions under the reaction system reflected that DMSO provided the best result (**details in SI, table S3**). Next, we investigated various light sources (different LEDs) and found that purple LED was more efficient in comparison to other light sources (**details in SI, table S1**). Finally, we monitored stoichiometric loading of phenyl iodide and K_3PO_4, and found that 2.0 equiv. of phenyl iodide and 2.5 equiv. of K_3PO_4 provided the optimum yield (entry 7-11, **table 1** and **other details in SI, table S4**).

After optimizing the reaction conditions, we examined the generality of the protocol by investigating the substrate scope with respect to *N*-methylquinoxalin-2(1*H*)-one (**Scheme 2**). The mono-substituted substrates with both electron-donating as well as electron-withdrawing groups at varied positions of the arene ring of *N*-methylquinoxalin-2(1*H*)-one such as -Me at 5 (**3ba**) and diastereomer product (**3ca**); -Cl at 5 (**3da**) and 6 (**3ea**), -CF_3 at 6 (**3fa**) and 7 (**3ga**) afforded acceptable yields (61-68%-**EDG,** 59-66%-**EWG**). Further, the present protocol was found to be compatible with the substrates having two electrons-withdrawing groups such as di-fluoro **3ha**, di-chloro **3ia**, and di-bromo, -chloro **3ja** (37-57% yields). Next, we turned our attention to examine the various substitutions at the nitrogen of *N*-quinoxalin-2(1*H*)-ones such as ethyl, 4-bromobenzyl, 2-oxo-2-phenylethyl,

allyl, and ethylacetate groups, delivering the respective products **3ka**, **3la**, **3ma**, **3na**, and **3oa** in average to good yields (44-76%). It's heartening to obscene that the groups sensitive to radicals, such as benzyl and allyl worked successfully in our case. However, the propargylic substitution at the nitrogen of *N*-quinoxalin-2(1*H*)-one was not compatible with the developed methodology since the corresponding substrate did not react to give the desired product **3pa** likely due to the presence of a terminal alkyne group.

Gratifyingly, the present methodology could be successfully applied to synthesize bioactive compounds. The *N*-substituted quinoxalin-2(1*H*)-ones (**1q** and **1r**) reacted smoothly with **2a** under the standard reaction conditions to access antitumor and antimicrobial (**3qa**) and ALR2 inhibitor agents (**3ra**) in 58 and 49% yields respectively (**Scheme 2**).

Subsequently, we investigated the applicability of our protocol for substituted aryl iodides and heterocyclic aryl iodides. Aryl iodides with electron-donating groups such as -Me at *m*- and *p*- (**3ab** and **3ac**), and -OMe at *p*- (**3ad**) position of the -Ph ring gave the desired product in good yields (56-65%) (**Scheme 3**). Further, aryl iodides possessing electron-withdrawing groups such as -Cl (**3ae**, **3af** and **3ag**), -Br (**3ah**), -CF_3 (**3ai**), benzoyl (**3al**), ester (**3am**), and -F (**3an** and **3ao**) at varied positions of the phenyl ring also proved viable substrates to deliver the required products in good yields (61-73%). Although a majority of these functionalities carried potential to participate in such reactions, however, in all these cases, the reaction was completely chemoselective and iodo group only reacted without fail. Likewise, di-substituted aryl iodides such as di-fluoro (**3aj**) and di-trifluoromethyl (**3ak**) reacted smoothly under the optimized reaction conditions (61-67%). Interestingly, the developed methodology was found to be fairly compatible with heterocyclic aryl iodides, including 4-iodopyridine (**3as**), 3-iodopyridine (**3ar**), 3-iodoquinoline (**3at**), and 2-iodothiophene (**3au**), as satisfactory yields of the corresponding products were obtained (30-73%), which dictates the broad substrate scope of our protocol. However, the protocol did not satisfactorily work in the case of substrates bearing acetyl at *p*- position, di-cyano, -CF_3 at *m*- and *p*-, -NO_2 at *p*- and 3-iodoindole derivatives (**3o**, **3p**, **3q** and **3v**), as an inseparable mixture of products was observed in each case.

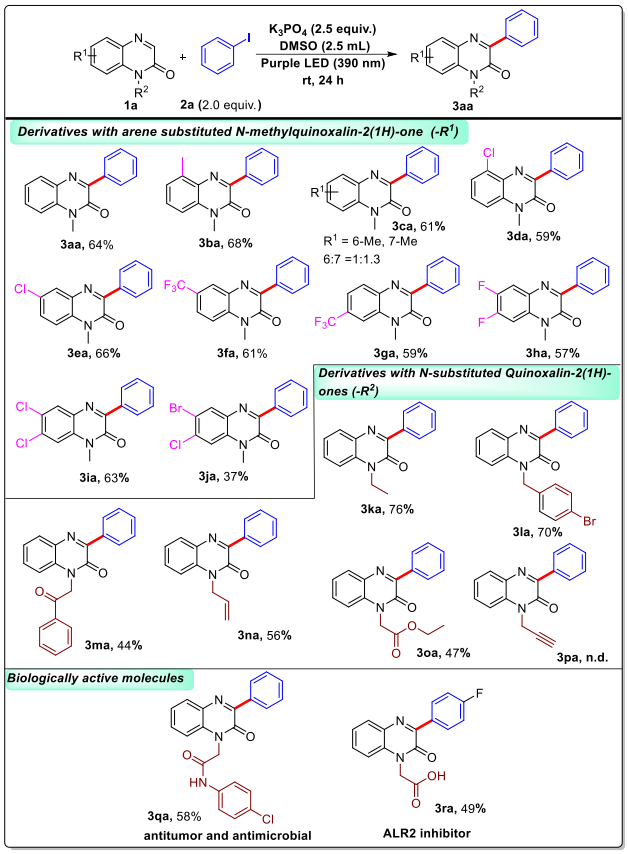


1a **2a** **3aa**

Entry	Light Source	Base (equiv.)	Solvent	Yield (%)[a]
1	Purple LED (390 nm)	Cs_2CO_3 (2)	DMSO	51
2	Purple LED (390 nm)	K_3PO_4 (2)	DMSO	53
3	Purple LED (390 nm)	K_3PO_4 (1)	DMSO	38
4	Purple LED (390 nm)	K_3PO_4 (1.5)	DMSO	45
5	Purple LED (390 nm)	K_3PO_4 (2.5)	DMSO	64
6	Purple LED (390 nm)	K_3PO_4 (3)	DMSO	66
7	Purple LED (390 nm)	K_3PO_4 (2.5)	DMSO	31[b]
8	Purple LED (390 nm)	K_3PO_4 (2.5)	DMSO	34[c]
9	Purple LED (390 nm)	K_3PO_4 (2.5)	DMSO	53[d]
10	Purple LED (390 nm)	K_3PO_4 (2.5)	DMSO	55[e]
11	Purple LED (390 nm)	K_3PO_4 (2.5)	DMSO	55[f]
12	Purple LED (390 nm)	-	DMSO	n.d.
13	-	K_3PO_4 (2)	DMSO	n.d.[g]
14	Dark	K_3PO_4 (2)	DMSO	n.d.
15	60°C	K_3PO_4 (2)	DMSO	n.d.
16	Sun light	K_3PO_4 (2)	DMSO	n.d.

Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol),) and base in solvent (2.5 mL) were irradiated with Purple LEDs (390 nm, 40 W) for 24 h at rt; [a]Yields determine using column chromatogrphay [b]**2a** (0.25 mmol); [c]**2a** (0.375 mmol); [d]**2a** (0.50 mmol); [e]**2a** (0.625 mmol); [f]**2a** (0.75 mmol); [g]without light.

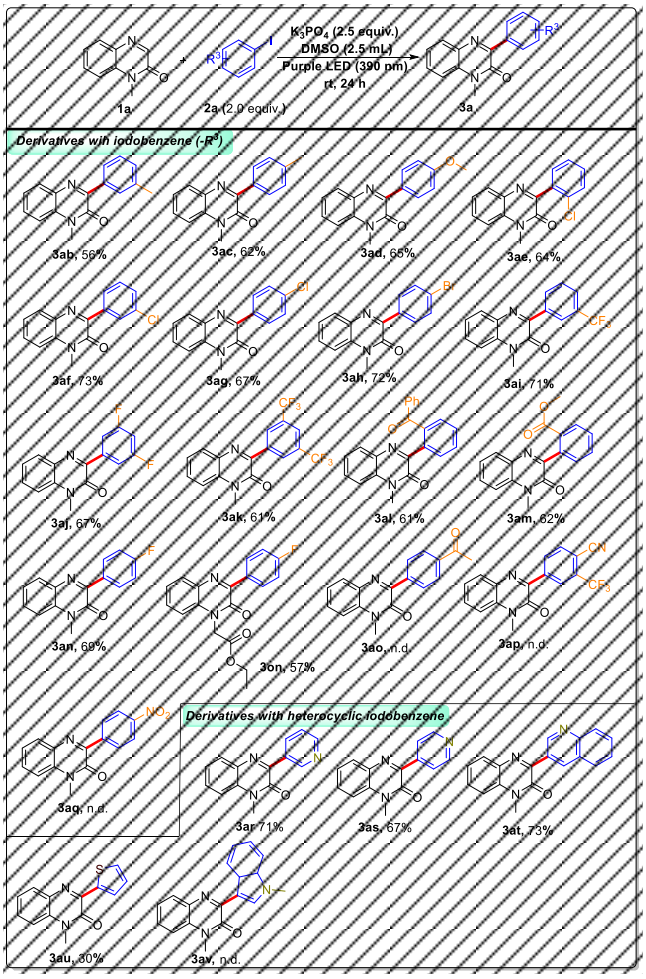
Table 1. Optimization of the reaction conditions.



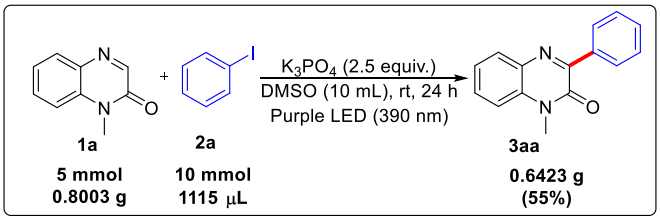
Scheme 2. Substrate Scope of *N*-methylquinoxalin-2(1*H*)-one.

Pleasingly, the methodology could also be applied to a scale-up synthesis using **1a** (5 mmol) and **2a** (10 mmol) as substrates and obtained 0.64 g of the desired product **3aa** in 55% yield (**Scheme 4**).

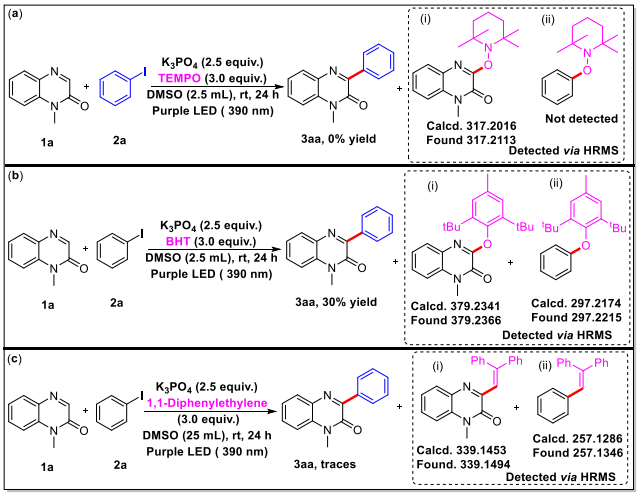
To throw light on the reaction mechanism, a series of control experiments were performed to elucidate the reaction pathway (**Scheme 5)**. The radical scavenging experiments revealed that the reaction was completely quenched with TEMPO (3 equiv.) (2,2,6,6-tetramethyl-1-piperidinyloxy) to give the adduct **a(i)** (confirmed *via* HRMS), while, adducts **b/c(i)** and **b/c(ii)**, were detected with BHT (3 equiv.) and 1,1 diphenylethylene (3 equiv.) respectively (**Scheme 5a/b/c**). Furthermore, the radical signal was detected in the reaction mixture *via* EPR-spectroscopy (**g = 2.0041**). In addition, to ascertain whether radical generation was happening between **1a** and base or **2a** and base, interestingly, radical signal was detected between **1a** and base. Therefore, indicating that the event of SET between **1a** and base upon irradiation (**details in SI, figure S6**).
The absence of Pd, Cu, or any other transition metal in K_3PO_4 was confirmed by XPS studies, indicating the lack of any transition metal-assisted coupling possibility (**details in SI, figure S8**). Next, the mixing of **1a** and K_3PO_4 gave a coloured solution, implying a bathochromic shift and this was confirmed *via* UV/Vis-spectroscopic studies (**details in SI, figure S3**). However, it was equally clear from the UV/Vis-spectroscopic studies that **2a** has no role in formation of light absorbing species in this reaction (**Figure S7**) Later, the quantum yield calculations corroborated that the reaction mechanism was not proceeded *via* chain pathway (**ϕ = 0.75**).



Scheme 3. Substrate scope of aryl/ heteroaryl iodides.



Scheme 4. Scale-up synthesis.



Scheme 5. Control experiments.

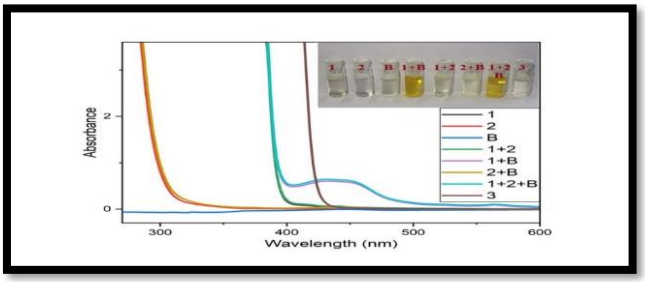
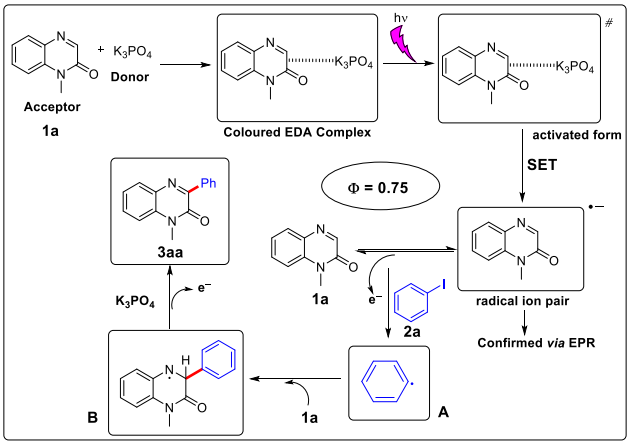


Figure 2. UV-Visible spectra of substrates.

After the analysis of control experiments and previous relevant literature reports,[16] a tentative reaction mechanism has been proposed in Scheme **6**. In the reaction mechanism, the quinoxalin-2(1*H*)-one (**1a**) and K_3PO_4 form a coloured EDA-complex, which upon photoexcitation and followed by a single electron transfer (**SET**) process (from K_3PO_4 to quinoxalin-2(1*H*)-one) to give the radical ion pair. Subsequently, the generated radical ion pair reduce the aryl halide to furnish the aryl radical (**A**), followed by radical addition to the quinoxalin-2(1*H*)-one (**1a**), to generate a radical species (**B**), which upon a SET, followed by deprotonation to give the desired product **3aa**.



Scheme 6. Plausible mechanism.

Conclusion: -

In summary, we have accomplished EDA-mediated C-3 arylation of quinoxalin-2(1*H*)-ones using aryl/heteroaryl iodide as an aryl radical precursor under remarkably mild and effective conditions. The method has worked well for both electron-donating and electron-withdrawing groups in case of quinoxalin-2(1*H*)-ones as well as aryl/heteroaryl iodides to furnish the desired products in moderate to good yields. Also, we have performed several relevant mechanistic experiments such as UV/Vis-spectroscopy, radical-trapping experiments, EPR spectroscopic studies, and quantum yield calculations, to understand the reaction mechanism. These experiments revealed that C-3 arylation of quinoxalin-2(1*H*)-ones happened *via* a SET process.

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Notes

The authors have no conflicts of interest.

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