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ARTICLE

Visible-light-accelerated amination of quinoxalin-2-ones and benzo[1,4]oxazin-2-ones with dialkyl azodicarboxylates under metal and photocatalyst-free conditions.

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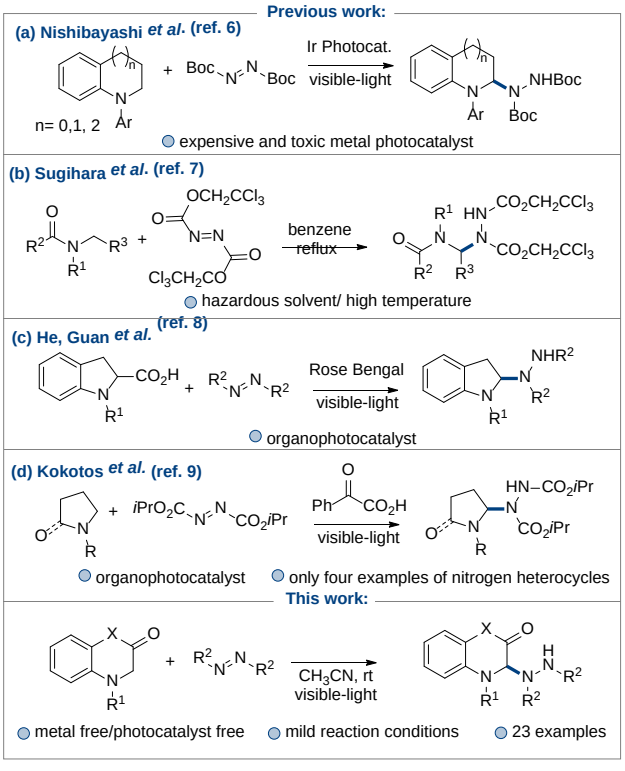
A direct sp³ C-H amination of cyclic amines (dihydroquinoxalinones and dihydrobenzoxazinones) with dialkyl azo dicarboxylates accelerated by visible-light irradiation is described under metal and photocatalyst-free conditions. This protocol features a very mild reaction conditions for the synthesis of aminal quinoxaline and benzoxazine derivatives with good to high yields (up to 99%). These aminal derivatives respresent versatile building blocks for the divergent synthesis of quinoxalin-2-one derivatives.

Introduction

The oxidative C(sp³)-H bond functionalization at α-position of heteroatoms is a special topic that have received a huge attention from the synthetic organic community.[1] In this context, the direct transformation of C-H bond to a C-N bond is one of the most interesting methodologies for the functionalization of heterocycles, extremely important for medicinal chemistry and pharmaceutical industry.[2] Researchers are constantly searching for expanding the functionalization of heterocycles, specially nitrogen heterocycles, with novel functionalization models. However, most of examples described in the literature are metal-catalyzed processes and therefore, the development of metal-free protocols for the transformation of C-H bonds to a C-N bonds that improve the sustainability of the chemical process is highly desirable.

Dialkyl azodicarboxylates have been recognized as useful electrophiles and have been employed as essential electrophilic reagents in the Mitsunobu reaction.[3] In the last years, the oxidative C(sp³)-H bond functionalization at α-position of nitrogen in *N*-heterocycles using dialkyl azodicarboxylates have been described (Scheme 1).[4,5] Nishibayashi, in 2012, described the C-H amination of tetrahydroquinoline and indoline derivatives with di-*tert*-butyl azodicarboxylate using an iridium photocatalyst and visible-light.[6] Honzawa and Sugihara, in 2014, reported the metal and catalyst-free amination of tertiary amines using bis-(2,2,2-trichloroethyl) azodicarboxylate in benzene at reflux.[7] While Guan and He described the photocatalytic decarboxylative amination of indoline-2-carboxylic acids with dialkyl azodicarboxylates using Rose Bengal as photocatalyst.[8] More recently, Kokoto's group described the functionalization of pyrrolidines and pyrrolidin-2-ones with di-isopropyl azodicarboxylate (DIAD) using phenylglyoxylic acid as photocatalyst under the irradiation of visible-light.[9]



Scheme 1. Direct C(sp³)-H amination of cyclic amines.

Despite of these successful examples of direct amination of nitrogen heterocycles, the development of new methodologies to expand the scope to other cyclic amines (*N*-heterocycles) is highly desirable from the synthetic point of view. In particular,

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dihydroquinoxalinones[10] and dihydrobenzoxazin-2-ones[11] constitute a prevailing scaffolds frequently found in many biologically active natural and pharmaceutical agents (Figure 1).[12,13] Therefore, their functionalization using environmentally friendly methods could be significant and interesting for medicinal chemistry. Herein, continuing with our interest in the functionalization of cyclic amines,[14] we report the first metal-free and photocatalyst free direct amination of quinoxalinones and benzoxazinones with azodicarboxylate esters mediated by visible-light. The corresponding aminal products constitute useful building blocks for divergent synthesis of these particular nitrogen heterocycles, making the present methodology highly valuable for the synthetic community.

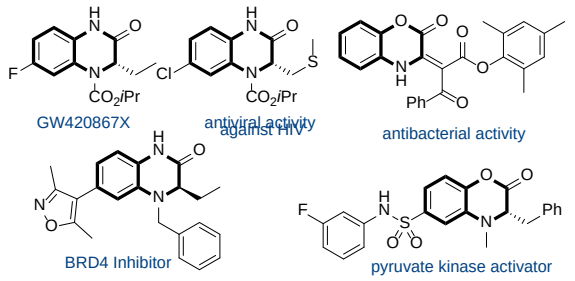
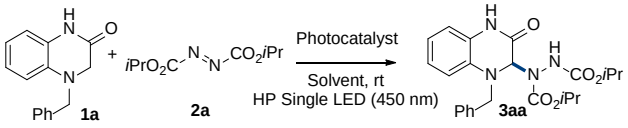


Figure 1. Biologically active quinoxalin-2-one and benzoxazin-2-one derivatives.

Results and discussion

To optimize the reaction conditions, 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**1a**) and di-*iso*-propyl azodicarboxylate (DIAD) (**2a**) were chosen as model substrates (Table 1). The initial reaction using 1 mol % $Ru(bpy)_3Cl_2$ under irradiation of HP Single LED (450 nm) at room temperature, acetonitrile as solvent and under argon atmosphere afforded the corresponding aminal product **3aa** in 99% excellent yield after 3 hours (entry 1). Other photocatalysts ($Ir(ppy)_3$, Rose Bengal, Eosin Y, Fukuzumi's photocatalyst and 9,10-phenanthrenedione) were evaluated (entries 2-6), obtaining lower yields with longer reaction times. Then, different solvents such as CH_2Cl_2, THF and DMF were evaluated (entries 7-9). In CH_2Cl_2 and THF, the amination of **1a** was very slow and low conversions were observed, while with DMF, the reaction was similar than with CH_3CN, but obtaining the corresponding product **3aa** with a slightly lower yield (86%). Changing the molar ratio of reagents **1a** and **2a**, speeded the reaction without compromising the yield (entry 10). Finally, several control experiments were carried out. When the reaction was carried out without photocatalyst (entry 11), we obtained the amination product **3aa** with excellent yield (99%). While the reaction performed under darkness (entry 13), gave the corresponding product in 91% yield but increasing the reaction time from 2 to 24 hours. This results revealed that the visible-light is not essential for the direct amination of **1a**, although the irradiation with HP single Blue LED speeded the reaction, observing higher conversions in shorter reaction times. In order to develop a more sustainable protocol, we decided to study the scope of the reaction using conditions presented in entry 11 of Table 1.

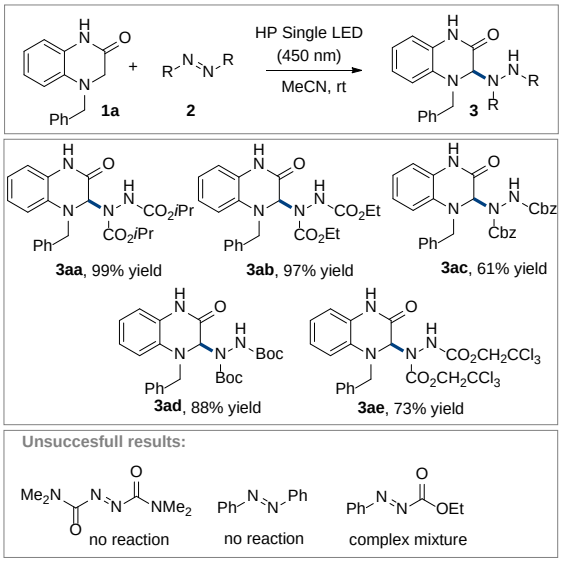
Table 1 Optimization of the reaction conditions.[a]



Entry	PC (%)	Solvent	t (h)	Yield (%)[b]
1	$Ru(bpy)_3Cl_2$ (1)	MeCN	3	99
2	$Ir(ppy)_3$ (1)	MeCN	23	55
3	Rose Bengal (5)	MeCN	23	50
4	Eosin Y (5)	MeCN	23	65
5	Fukuzimi's catalyst (5)	MeCN	18	73
6	9,10-phenanthrenedione (5)	MeCN	20	30
7	$Ru(bpy)_3Cl_2$ (1)	CH_2Cl_2	24	<5
8	$Ru(bpy)_3Cl_2$ (1)	THF	24	<5
9	$Ru(bpy)_3Cl_2$ (1)	DMF	2	86
10[c]	$Ru(bpy)_3Cl_2$ (1)	MeCN	1,5	98
11[c]	-	MeCN	2	99
13[c,d]	-	MeCN	24	91

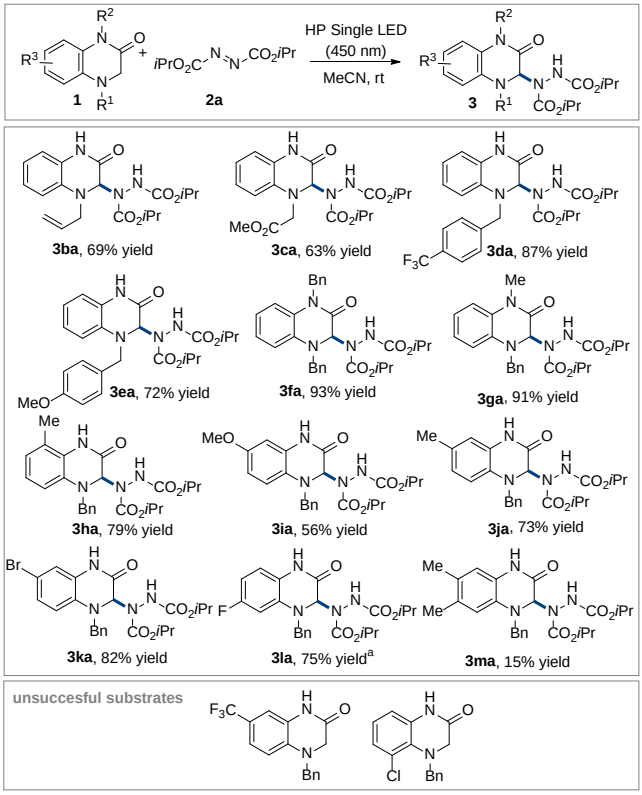
[a] Reaction conditions: **1a** (0.13 mmol), **2a** (0.1 mmol) and photocatalyst (X mol%) were dissolved in 1mL of solvent and stirred at rt under Ar atmosphere and irradiation of HP Single LED (450 nm). [b] Yield after purification by column chromatography. [c] The reaction was performed with **1a** (0.1 mmol) and **2a** (0.13 mmol). [d] Reaction performed under darkness.

First, we evaluated the reaction scope regarding the azodicarboxylate esters **2** (scheme 2). For example, diethyl azodicarboxylate (DEAD) readily participates in this reaction, affording the amination product **3ab** in 97% yield. *N*-Cbz and *N*-Boc groups are tolerated, obtaining the corresponding aminal products with good yields. Finally, when the reaction was performed with bis(2,2,2-trichloroethyl) azodicarboxyate, product **3ae**, was gained with 73% yield. Unfortunately, we did not observe conversion when either *N,N,N,N*-tetramethyl azodicarboxyamide or azobenzene were used, probably due to their lower electrophilicity.



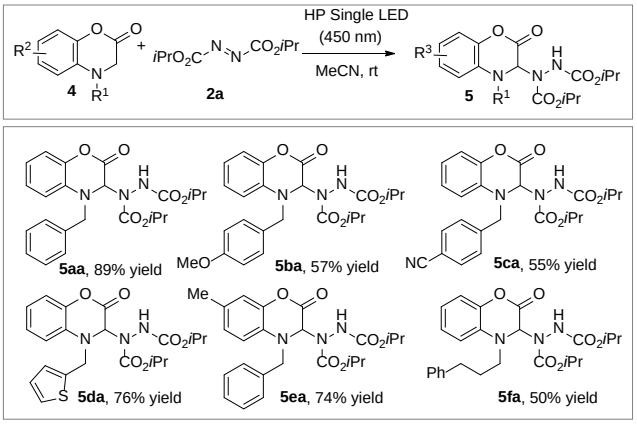
Scheme 2. Scope of the C(sp^3)-H amination regarding the azodicarboxylate esters. Reaction conditions: **1a** (0.1 mmol) and **2** (0.13 mmol) in 1mL of CH_3CN and stirred at rt under Ar atmosphere and irradiation of HP Single LED (450 nm).

After studying the scope of the reaction with **1a**, we focused our attention in the reaction with different dihydroquinoxalin-2-ones (Scheme 3). First, we evaluated the effect of the protecting group at the nitrogen of the amide of dihydroquinoxalin-2-one **1**. Our protocol tolerated several groups at the nitrogen atom, such as benzyl, allyl or CH_2CO_2Me, affording the corresponding aminated quinoxalines **3** with good yields. Moreover, the methodology tolerates different benzylic substituents bearing either electron-donating or electron-withdrawing groups, affording the products **3da** and **3ea** with high yields. 1,4-disubstituted-3,4-dihydroquinoxalin-2-ones could be used under the optimized reaction conditions and product **3fa** and **3ga** was obtained with excellent yields (93% and 91%, respectively). 3,4-Dihydroquinoxalin-2-ones bearing electron-donating (Me, MeO) or electron-withdrawing (Br, F) groups at different positions on the aromatic ring furnished the corresponding products in good yields (56–82%), regardless of the position or the electronic character of the substituents. However, if the substituent is a strong electron-withdrawing group (CF_3) we did not observe reaction as well if the substituent is at 5-position (Cl).



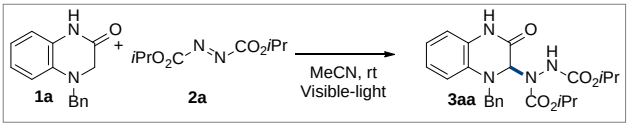
Scheme 3. Scope of the C(sp^3)-H amination regarding the dihydroquinoxalin-2-one derivatives **3**. Reaction conditions: **1** (0.1 mmol) and **2a** (0.13 mmol) in 1mL of CH_3CN and stirred at rt under Ar atmosphere and irradiation of HP Single LED (450 nm). [a] Reaction at 0.5 mmol scale.

Dihydrobenzoxazin-2-one scaffold is also present in a big number of biologically active molecules and natural products. Consequently, we decided to apply our metal-free direct amination methodology to this nitrogen heterocycle (Scheme 4). Delightfully, 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one **4a** reacted efficiently and the corresponding functionalised benzoxazinone **5aa** was obtained with 89% yield (Scheme 4). However, if the reaction was performed in the absence of visible-light, we did not observe conversion to product **5aa** after 24 hours. In a similar way, several 3,4-dihydrobenzoxazin-2-one derivatives bearing different substitutional patterns at the benzylic substituent or in the aromatic ring were tested under the optimized reaction conditions obtaining the corresponding aminals **5** with moderate to good yields (50-76%).



Scheme 4. Scope of the C(sp^3)-H amination regarding the dihydrobenzoxazin-2-one derivatives **4**. Reaction conditions: **4** (0.1 mmol) and **2a** (0.13 mmol) were dissolved in 1mL of CH_3CN and stirred at rt under Ar atmosphere and irradiation of HP Single LED (450 nm).

To further showcase the practicability, scalability and sustainability of this protocol, we performed the direct C(sp^3)-H amination at one-gram scale using sunlight irradiation (Scheme 5, entry 1). Under these conditions, we obtained the product **3aa** in high yield (88%). We further scale up the reaction to two-gram scale using Blue LEDs irradiation obtaining high yields (90% and 83%).

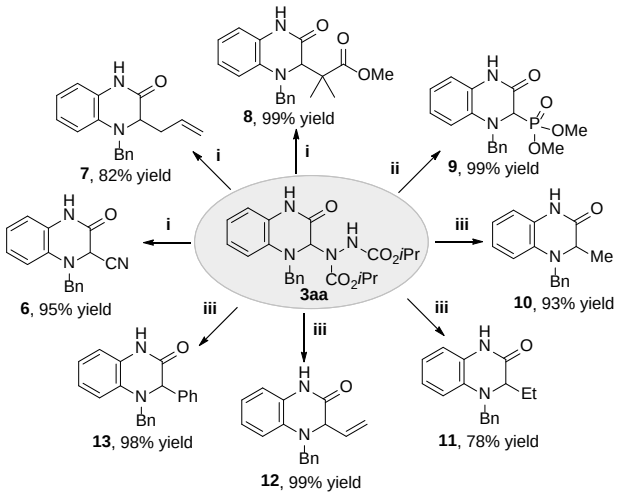


Entry	Source of light	1a	3aa (yield%)
1	sun-light	3.8 mmol, 0.92 g	3.34 mmol, 1.47 g (88% yield)
2	Blue LEDs (450 nm)	5 mmol, 1,2 g	4.5 mmol, 1.98 g (90% yield)
3	Blue LEDs (450 nm)	6,6 mmol, 1.57 g	5.47 mmol, 2.41 g (83% yield)

Scheme 5. Gram scale reactions using sun-light or Blue LEDs.

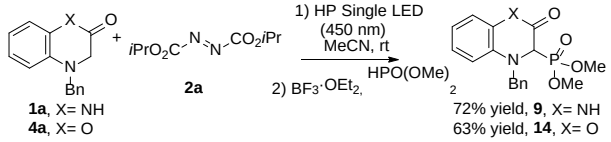
The divergent syntheses of complex molecules from a common intermediate have attracted enormous attention in the chemical community in the past few years because it can improve the efficiency of chemical synthesis, and therefore the sustainability in the chemical processes.[15] Aminals are useful building blocks for nitrogen-containing compounds due to their high reactivity toward nucleophilic substitution reactions at α-position of the nitrogen. We envisioned that our aminated

products **3** and **5** could be excellent intermediates for the divergent synthesis of a wide range of quinoxalin-2-one and benzoxazin-2-one derivatives with different substitution pattern at 3-position. Therefore, compound **3aa** was subjected to several nucleophilic substitutions reactions with different nucleophiles (Scheme 6). For example, aminal **3aa** was subjected to a Strecker reaction with TMSCN in the presence of $BF_3{\cdot}OEt_2$, obtaining the α-aminonitrile **6** with 95% yield. In a similar way, the reaction with allyltrimethylsilane and α-dimethyl ketene silyl acetal, afforded the corresponding functionalized dihydroquinoxalin-2-one derivatives **7** and **8** with excellent yields. Other nucleophiles such dimethyl phosphonate reacted successfully to afford the corresponding phosphonate **9** in quantitative yield (99%). Moreover, we applied Grignard reagents as nucleophiles with the aminal **3aa**, but in these cases the reactions did not require the use of $BF_3{\cdot}OEt_2$. Methyl, ethyl, vinyl and phenyl-magnesium bromides as a sp^3 and sp^2 carbon nucleophiles afforded the corresponding products **10**-**13** in high yields, showing the versatility of the corresponding aminated quinoxalinones obtained with our methodology.



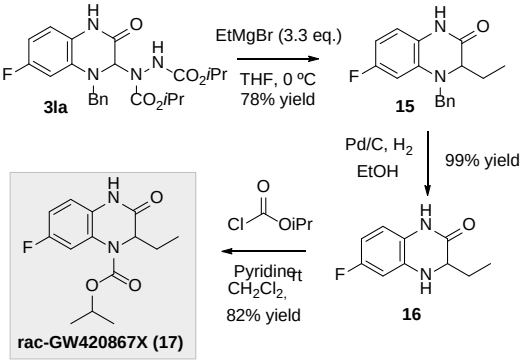
Scheme 6. Syntethic transformations of **3aa**. Divergent synthesis of dihydroquinoxalin-2-one derivatives. Reaction conditions: **i** TMS-Nu (3 eq.), $BF_3{\cdot}OEt_2$ (1,1 eq.) and **3aa** (0.1 mmol) in MeCN. **ii** $(CH_3O)_2OPH$ (3 eq.), $BF_3{\cdot}OEt_2$ (1,1 eq.) and **3aa** (0.1 mmol) in MeCN. **iii** RMgBr (3.3 eq.) and **3aa** (0.1 mmol) in THF at 0 ºC.

The one-pot synthesis of an organic compound in the same reaction vessel is widely considered to be an efficient approach in synthetic organic chemistry. We also wanted to apply our methodology for the one-pot functionalization of cyclic amines (Scheme 7). Delightful, we could obtain compounds **9** and **14** with good yields, after the addition of $BF_3{\cdot}OEt_2$ and dimethyl phosphonate.



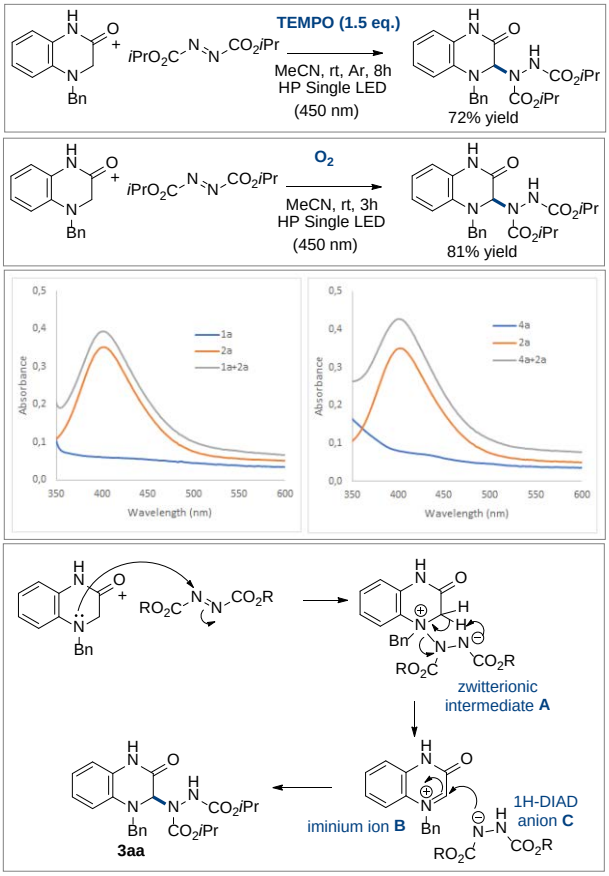
Scheme 7. One-pot functionalization of dihydroquinoxalin-2-one **1a** and dihydrobenzoxazin-2-one **4a**.

Finally, we wanted to demonstrate the utility of this method through the straightforward synthesis of rac-GW420867X (**17**),[12f] a non-nucleoside reverse transcriptase inhibitor (Scheme 8). Aminated dihydroquinoxalin-one **3la** was reacted with EtMgBr to afford quinoxalin-2-one **15** in 78% yield. Compound **15** was catalytically deprotected using H_2 and 10% Pd/C in EtOH, and then, the reaction with isopropyl chloroformate in the presence of pyridine, allowed us to obtain the biologicaly active compound rac-GW420867X (*rac*-Opaviraline) (**17**) in 82% yield.



Scheme 8. Synthesis of antiviral GW420867.

To gain insight into the reaction mechanism, we conducted a series of control experiments (Scheme 9). The reaction in the presence of 1.5 equiv of TEMPO afforded 72% yield of **3aa**, while if the reaction was run under oxygen atmosphere, aminal **3aa** was obtained in 81% yield, clearly indicating that radical intermediates are not present under the reaction conditions. Nevertheless, we observed that visible-light accelerates the reaction in the case of quinoxalin-2-ones, while in the case of benzoxazin-2-ones is necessary to observe conversion to aminal **5**. We have performed several experiments in order to determine if a EDA complex is formed. We observed an increase in the absorbance but without a bathochromic shift.[16,17] What we think is that blue-light activates the azodicarboxylate derivatives. A pausible mechanism is depicted in Scheme 9. The zwitterionic intermediate **A** could be formed by a nucleophilic addition of the amine to DIAD. After, the iminium ion **B** is generated through the dehydrogenation of **A** realeasing the 1H-DIAD anion **C**. Finally, the nucleophilic atack of anion **C** to the iminiun ion affords aminal **3aa**.



Scheme 9. Pausible reaction mechanism.

Conclusions

In summary, we have developed a direct C(sp^3)-H amination of 4-substituted-3,4-dihydroquinoxalin-2-one and 4-substituted-3,4-dihydrobenzoxazin-2-one derivatives with dialkyl azodicarboxylates accelerated by visible-light in a metal-free and photocatalyst-free protocol. The corresponding aminal products were obtained with good to excellent yields under very mild reaction conditions. The reaction is scalable to more than 5 mmol scale using Blue LEDs or sun-light irradiation obtaining the corresponding aminated quinoxalin-2-one **3aa** with high yields. These aminal derivatives represent versatile and useful building blocks for the divergent synthesis of quinoxalin-2-one derivatives. Moreover, the present methodology has been successively applied to a concise synthesis of the biologically active compound rac-GW420867X and therefore might find more applications in organic synthesis and pharmaceutical development.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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