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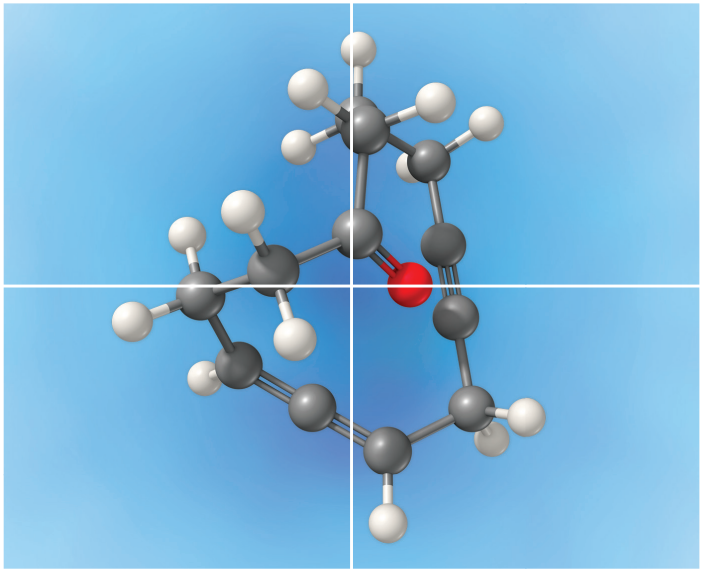

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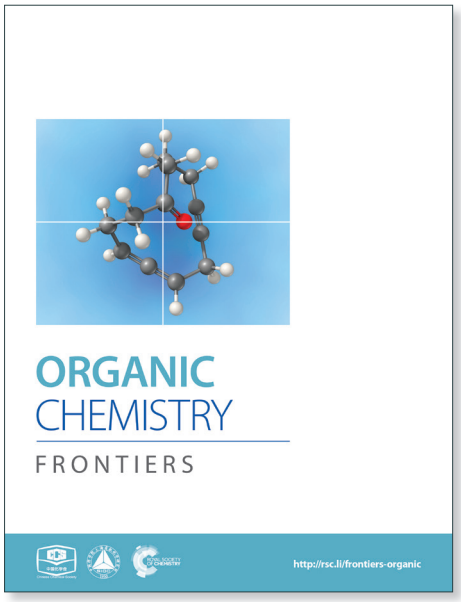

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Journal Name

ARTICLE

Visible-light photoredox catalysis: direct synthesis of fused β-carbolines through oxidation/[3+2] cycloaddition/oxidative aromatization reaction cascade in batch and flow microreactors

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Fused β-carbolines were synthesized *via* a visible light photoredox catalyzed oxidation/[3+2] cycloaddition/oxidative aromatization reaction cascade in batch and flow microreactors. Several structurally diverse heterocyclic scaffolds were obtained in good yields by coupling of tetrahydro-β-carbolines with a variety of dipolarophiles under photoredox multiple C-C bond forming events. The photoredox coupling of tetrahydro-β-carboline with 1,4-benzoquinone was significantly faster in continuous flow microreactor and the desired products were obtained in higher yields compared to batch reactor.

Introduction

Structurally novel and multifarious heterocycles are very important in drug discovery program for screening new hits against biological targets. Development of efficient synthetic transformations that allow construction of complex molecular frameworks from relatively simple and easily accessible starting materials in atom economical and multiple bond forming events involving one-pot operations is very challenging. β-Carbolines are amongst the most important biologically valuable scaffolds found in a plethora of synthetic and natural products of medicinal significance.[1] Many marine organisms, mammalian tissues and body fluids, plants, and insects contain numerous alkaloids or hormones having a β-carboline core unit (Figure 1).[1,2] β-Carboline containing molecules possess numerous biological activities such as antineoplastic,[2] antimalarial,[3a] antimicrobial,[3b] antithrombotic,[3c] hypnotic and anxiolytic,[3d,e] anticonvulsive,[3f] and anti-inflammatory.[3g] Therefore, constructing structurally novel libraries of fused β-carboline derivatives through efficient synthetic strategies has become an important task.[4] In recent years, considerable attention has been focused over the development of the clean and sustainable energy mediated synthetic strategies due to the exhaustion and non-renewability of fossil fuels. In these perspectives, visible light photoredox catalysis[5] has been found as a promising alternative approach. Despite the significant advances in this field, full spectrum of the synthetic utility of visible light photoredox catalysis is yet to be explored.

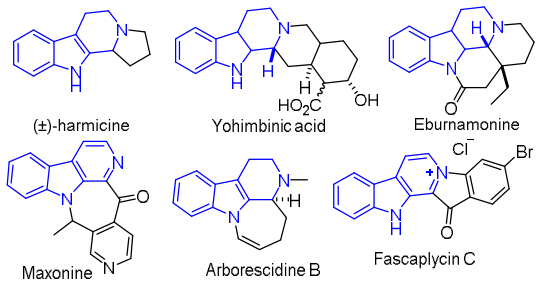

Figure 1. A few examples of natural products containing β-carboline.

A careful survey of literature revealed that most of the photoredox catalysis deals with the funtionalization of the relatively unreactive C–H bonds adjacent to N-atoms and a single C-C bond is formed in overall process. Examples of photoredox catalysis, where multiple C-C bonds are formed, are only a few.[6] As a part of our research program towards the development of newer heterocyclic libraries of medicinal importance,[7] herein we report the construction of fused β-carbolines *via* photoredox catalyzed oxidation/[3+2] cycloaddition/oxidative aromatization reaction cascade in batch and flow microreactors (Scheme 1). Tetrahydro-β-carbolines were functionalized in multiple C-C bond forming events that proceeded *via* photoredox generation of azomethine ylides and subsequent [3+2] dipolar cycloaddition reaction. It is noteworthy that the synthetic strategy described herein does not require any additional step or reagent to yield aromatized products. Thus, an efficient, atom economical, and high yielding methodology involving oxidation, 1,3-dipolar cycloaddition, and aerobic oxidative aromatization for fused β-carbolines was developed.

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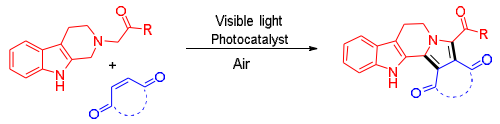
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

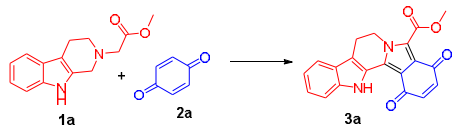


Scheme 1. Visible light photoredox catalyzed oxidation/[3+2] cycloaddition/oxidative aromatization reaction cascade for the synthesis of fused β-carboline derivatives

Results and discussion

At the onset, we commenced our investigations by exploring the coupling of methyl 2-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-b]indol-2-yl)acetate **1a** with 1,4-benzoquinone **2a**. The substrate **1a** was obtained by N-alkylation of tryptoline with methyl α-bromoacetate. Preliminary results revealed that in the presence of catalytic amount of the photoredox catalyst $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ and visible light (white LED) the aromatized cycloadduct **3a** could be obtained in good yields (Table 1).

Table 1. The effect of light, catalyst, and solvent over the coupling of **1a** and **2a** to yield **3a**.[a]



Entry	Light[b]	Photo-catalyst	Loading (mol%)	Time (h)	Yield of **3a** (%)[c]
1	√	--	--	48	ND
2	X	--	---	48	ND
3	√	$[Ru(bpy)_3Cl_2]\cdot 6H_2O$	1.0	12	68
4	X	$[Ru(bpy)_3Cl_2]\cdot 6H_2O$	1.0	48	ND
5	√	$[Ru(bpy)_3Cl_2]\cdot 6H_2O$	0.5	12	69
6	√	$[Ru(bpy)_3Cl_2]\cdot 6H_2O$	0.25	24	61
7	√	$Ru(bpy)_3(PF_6)_2$	0.5	12	69
8	√	Rose bengal	0.5	48	NI
9	√	Rose bengal	5	48	33
10	√	Rose bengal	10	48	30
11	√	Eosin Y	5	48	ND
12	√	Rhodamine B	5	48	ND
13[d]	√	$[Ru(bpy)_3Cl_2]\cdot 6H_2O$	0.5	12	69
14[e]	√	$[Ru(bpy)_3Cl_2]\cdot 6H_2O$	0.5	12	ND
15[e,f]	√	$[Ru(bpy)_3Cl_2]\cdot 6H_2O$	0.5	24	65

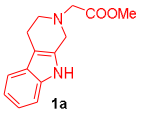
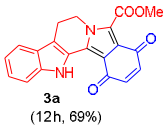
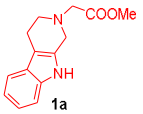
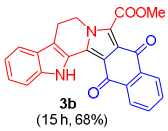
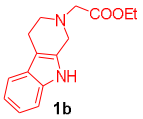
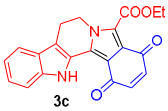
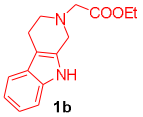
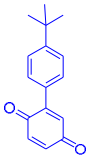
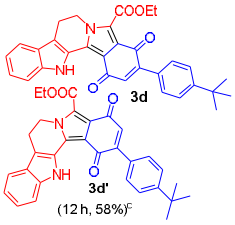
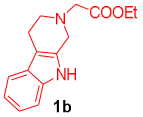
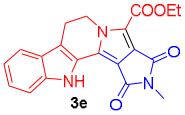
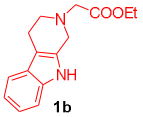
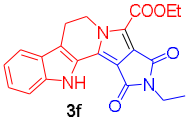
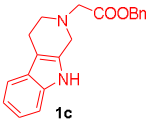
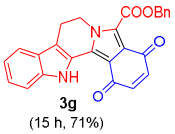
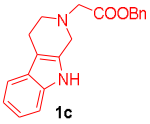
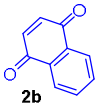
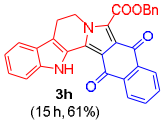
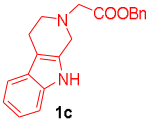
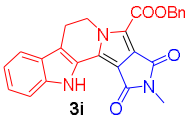
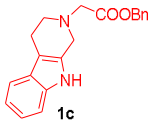
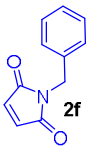
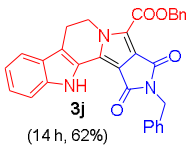
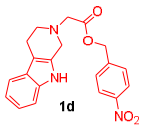
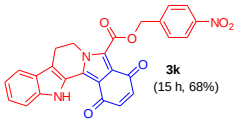
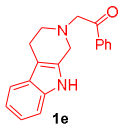
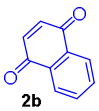
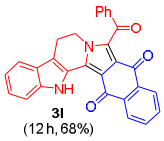
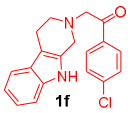
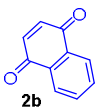
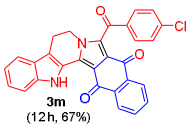
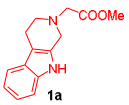
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), Photo-catalyst, MeCN (5 mL), air. [b]11W white LED bulb kept at a distance of 10 cm (approx.) from the reaction vessel. [c]Yields of the isolated products after column chromatography. [d]The reaction was done under oxygen atmosphere. [e]The reaction was done under nitrogen atmosphere. [f]t-BuOOH (10 eq.) was added to the reaction mixture. ND = The desired product was not detected on TLC. NI = Not isolated.

It was found that 0.5 mol% of $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ was sufficient to give high yields of **3a** in a reasonable reaction time (Table 1, entry 3, 5 & 6). $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ and $Ru(bpy)_3(PF_6)_2$ were equally effective for the reaction whereas the organic dyes (Rose Bengal, Eosin Y, Rhodamine B) were less effective (Table 1, entry 5, 7, 8, 11 & 12). Among the organic dyes screened, rose Bengal was somewhat effective but at higher loadings (Table 1, entry 8, 9, 10). Performing the reaction under oxygen atmosphere did not improve the product yield whereas no product was obtained when the reaction was performed under nitrogen atmosphere (Table 1, entry 13, 14). However, even under nitrogen atmosphere, a good yield of the desired product **3a** was could be obtained using t-BuOOH as an oxidant for the reaction (Table 1, entry 15).

Having the optimal reaction conditions at hand, generality of the reaction was investigated (Table 2). The scope of the tetrahydro-β-carboline was studied by taking methyl, ethyl, benzyl, *p*-NO_2-benzyl esters of 2-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-b]indol-2-yl)acetate (**1a-d**) and ketones (**1e-f**). The scope of the dipolarophile was studies by taking 1,4-benzoquinone (**2a**), 1,4-naphthoquinone (**2b**), 2-[4-(1,1-dimethylethyl)phenyl]-2,5-cyclohexadiene-1,4-dione (**2c**), N-methylmaleimide (**2d**), N-ethylmaleimide (**2e**), and N-benzylmaleimide (**2f**). The reaction was found to work well with a variety of β-carbolines and dipolarophiles. In most of the cases, the reaction gave good yields of the fused β-carbolines (**3a-n**). As expected, the reaction of tetrahydro-β-carboline **1b** with 2-[4-(1,1-dimethylethyl)phenyl]-2,5-cyclohexadiene-1,4-dione **2c** gave two products in nearly 1:1 ratio whose structures were tentatively assigned as **3d** (28%) and **3d'** (30%). In both the products (**3d**/**3d'**), the less substituted double bond of the quinone dipolarophile underwent cycloaddition with the azomethine ylide. Using diethylacetylene dicarboxylate **2g** as a dipolarophile, the reaction yielded a partly oxidised product **3n** under standard conditions (Table 2, entry 14). Structural elucidation and relative stereochemical assignments of **3n** was done by 2D DQFCOSY, NOESY and HSQC experiments. However, when the reaction of diethylacetylene dicarboxylate was conducted under oxygen atmosphere, it gave very good yield of desired aromatized product **3o** (Table 2, entry 15). The product **3o** was also obtained in fairly good yield using the standard reaction condition (under air) for extended period of time (Table 2, entry 16). β-Nitrostyrenes and ethyl acrylate were not found as good dipolarophiles for the reaction as they gave complex reaction mixtures under our standard conditions.

All the reactions gave several spots on TLC at the beginning but after longer reaction run a clean spot (corresponding to our desired product) appeared on TLC and by-products were minimized. Although moderate to good yields (58-80%) of the desired products were obtained, no other by-product could be isolated using column chromatography and characterized. In other similar photoredox [3+2] cycloadditions, an external oxidant (other than O_2) is required to get aromatized products.[6] However, it is noteworthy that most of the reaction we performed yielded aromatized products using air as the green oxidant. It is also noticeable that the reaction is compatible with tetrahydro-β-carbolines containing a free amine (NH) group, therefore all the products can be derivatized easily through N-alkylation/acylation.

Table 2. Evaluation of the substrate scope.[a]

Entry	Tetrahydro-β-carboline **1**	Dipolarophile **2**	Product **3**; Rxn. Time; Yield (%)[b]
1			 **3a** (12 h, 69%)
2			 **3b** (15 h, 68%)
3			 **3c** (10 h, 69%)
4			 **3d** + **3d'** (12 h, 58%)[c]
5			 **3e** (12 h, 61%)
6			 **3f** (12 h, 66%)
7			 **3g** (15 h, 71%)
8			 **3h** (15 h, 61%)
9			 **3i** (12 h, 64%)
10			 **3j** (14 h, 62%)
11			 **3k** (15 h, 68%)
12			 **3l** (12 h, 68%)
13			 **3m** (12 h, 67%)
14			**3n** (12 h, 65%)
15[d]			**3o** (10 h, 80%)
16			**3o** (36 h, 61%)

[a] Reaction conditions: Tetrahydro-β-carboline **1** (0.1 mmol), dipolarophile **2** (0.1 mmol), $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ (0.5 mol%), MeCN (5 mL), 11W white LED bulb, air. [b] Yields of the isolated products after column chromatography. [c] Combined yield for **3d** (28%) and **3d'**(30%). [d] The reaction was done under oxygen atmosphere.

In the past decade, continuous flow microreactors received considerable attention for performing organic transformation in safer and efficient ways.[8] Due to their small dimensions, microreactors are associated with high heat and mass transfer efficiency, very high surface to volume ratio and enhanced illumination homogeneity. These features make microreactors a very good tool for photochemistry.[9] Considering these aspects, a continuous flow protocol for the photoredox catalyzed coupling of tetrahydro-β-carbolines with dipolarophile was developed. Handling gaseous reagents (oxygen), and precisely controlling their flow rates in segmented flow microfluidic conditions is somewhat tricky. Therefore, in order to have an operationally simple microfluidic set-up, we preferred t-BuOOH as an oxidant over

gaseous oxygen. The reagents, photo-catalyst and oxidant were introduced through two syringe pumps into a visible light transparent capillary microreactors (PFA tubing, Id = 500 µm, length = 5 m, volume = 0.98 mL) which was wrapped over a visible light source (11W white LED). Schematic illustration of the photochemical reaction in flow microreactor is depicted in the Figure 2. The results of this study are given in Table 3. The short length scale and high illumination homogeneity in the microreactor provide increased photon flux. It resulted in an acceleration of the coupling reaction; full conversion was observed in a residence time of 8 minutes (Table 3, entry 3). Moreover the yields were slightly better in microreactors (75%) than in batch conditions (69%). Decreasing the stoichiometry of oxidant (t-BuOOH) from 10 eq. to 5 eq. resulted in low yields of the desired product (Table 3, entry 5). The daily outcome of the flow reactor was calculated as 2.16 mmol of the product per day which shows that the microreactor has the potential for scale up production.

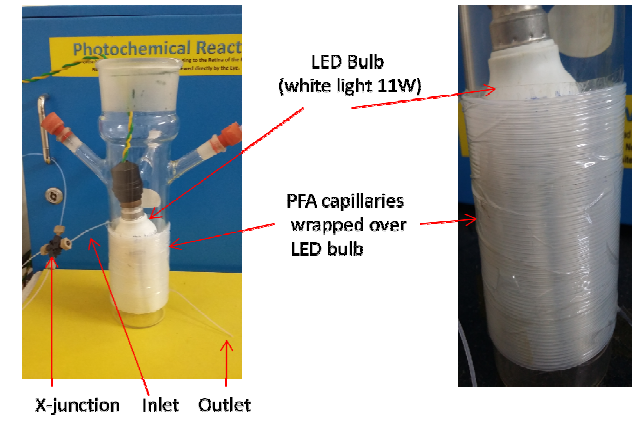


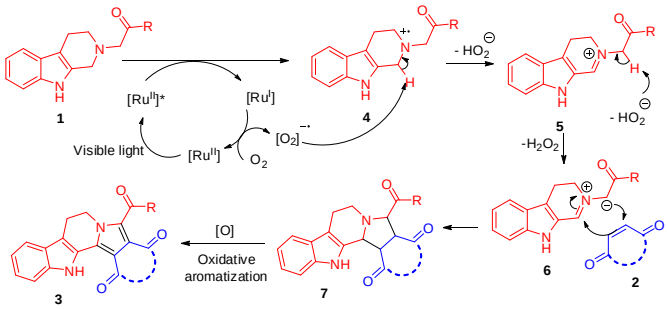
Figure 2. (a) Schematic illustration of the photoredox coupling in flow microreactors. (b) Picture of the capillary microreactor wrapped over visible light source (LED).

Table 3. The effect of flow rate/reaction time over the coupling of tetrahydro-β-carboline **1a** with 1,4-benzoquinone **2a** in flow microreactors.

Entry	Flow rate (µL/min)			Rxn. Time (m)	Yield of **3a** (%)[a]
	β-carboline **1a** & 1,4-benzoquinone **2a**	Photocatalyst	t-BuOOH		
1	200	200	80	2	25
2	100	100	40	4	60
3	50	50	20	8	75
4	25	25	10	16	75
5	50	50	10	9	55

[a] Yields of the isolated products after column chromatography

The formation of fused heterocycles through the photoredox coupling of tetrahydro-β-carbolines with dipolarophiles can be explained by a plausible mechanism depicted in Scheme 2. $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ gets activated by visible light and accepts an electron from β-carboline **1** to give a cation radical **4**. Next the intermediate **4** loses a proton to yield iminium ion **5** which further loses another proton to yield an azomethine ylide **6**. The azomethine ylide **6** undergoes 1,3-dipolar cycloaddition reaction with dipolarophile **2** to yield a cycloadduct **7** which readily aromatizes to final product **3**.



Scheme 2. A plausible mechanism for the visible light photoredox catalyzed oxidation/[3+2] cycloaddition/oxidative aromatization reaction cascade for the synthesis of fused β-carbolines

Conclusions

In conclusion, we have developed an efficient photoredox catalyzed oxidation/[3+2] cycloaddition/oxidative aromatization reaction cascade to yield structurally diverse heterocyclic frameworks. Multiple new C-C bonds were formed during the photoredox catalysis *via* generation of azomethine ylides from tetrahydro-β-carbolines followed by [3+2] cycloaddition reaction with a variety of dipolarophiles. The synthetic strategy we developed allows the formation of fused β-carboline derivatives in a manner that is atom economical, green and sustainable. The reaction efficiency was studied in batch and continuous flow microreactors. The use of continuous flow microreactors led to an improved irradiation over the reaction mixture, and offered considerably shorter reaction time and better yields of products compared to batch reactors.

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