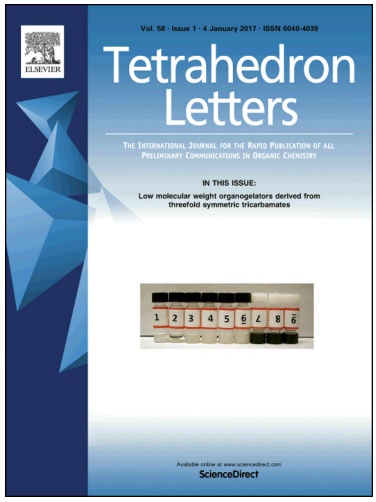
Accepted Manuscript



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PII: S0040-4039(17)30247-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.02.068
Reference: TETL 48679

To appear in: *Tetrahedron Letters*

Received Date: 6 January 2017
Revised Date: 20 February 2017
Accepted Date: 21 February 2017

Please cite this article as: Wu, G., Lv, T., Mo, W., Yang, X., Gao, Y., Chen, H., One-Pot Synthesis of Tricyclo-1,4-Benzoxazines Via Visible-Light Photoredox Catalysis In Continuous Flow, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.02.068

One-Pot Synthesis of Tricyclo-1,4-Benzoxazines Via Visible-Light Photoredox Catalysis In Continuous Flow

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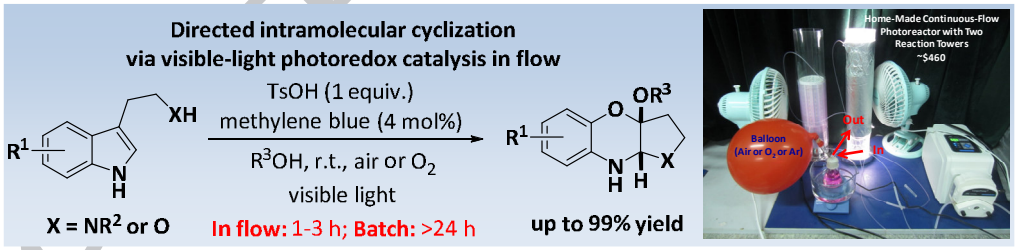
ABSTRACT: A facile one-pot synthesis of tricyclo-1,4-benzoxazines has been developed via metal-free intramolecular cyclization of indole derivates. These reactions were efficiently achieved at ambient temperature by using visible-light photoredox catalysis in continuous flow. This directed intramolecular cyclization could be easily handled and scaled up in an open flask, enabling construction of a focused compound library for further pharmacological evaluation.

Graphical Abstract



Keywords: *One-pot; Flow chemistry; Intramolecular cyclization; Metal-free; Room temperature*

Introduction

1,4-Benzoxazines as one of the common structural scaffolds ubiquitously exist in a large number of pharmacological compounds[1] which exhibit various fundamental biological functions including neuroprotective,[2] antitumor,[3] anti-inflammatory,[4] antithrombotic,[5-7] as well as antihypertensive effects.[8] In particular, some benzoxazines have been developed as antibacterial agents,[9,10] antipsychotic agents,[11] and cardiovascular drugs[12]. For example, levofloxacin (**Figure 1**) with 1,4-benzoxazine moiety exhibits excellent antibiotic activities against a range of bacteria.[13] Similar fragment is also found in the antiemetic agent azasetron which has been recognized as a typical member of 5-HT_3 receptor antagonists.[14] DIMBOA (2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one) is a naturally-occurring hydroxamic acid found in maize, which has the property of modifying the binding affinity of auxins to receptor sites.[15,16] More recently, our previous work by utilizing scaffold repurposing approach[17] has identified tricyclo-1,4-benzoxazine derivatives as potent anticancer agents with promising antiproliferative activities against various cancer cell lines.[18]

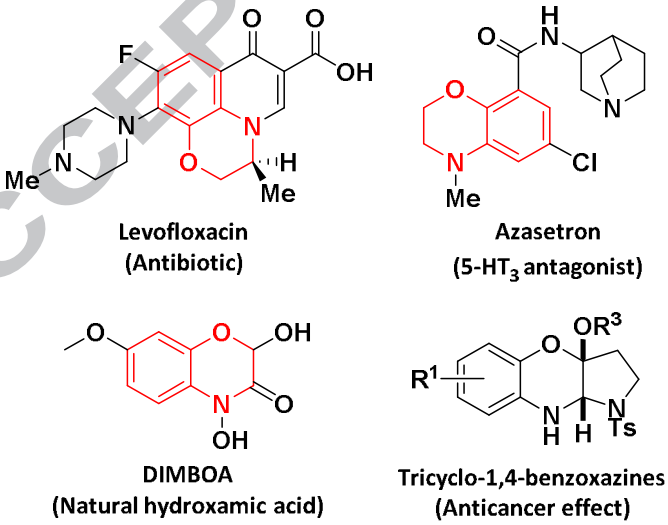


Figure 1. Representative 1,4-benzoxazine-containing pharmacological compounds.

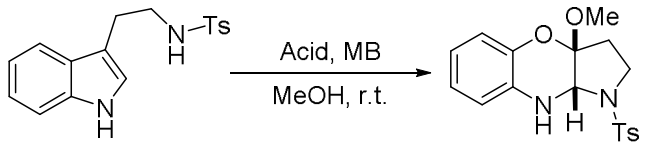
The extensive utility of 1,4-benzoxazines derives organic chemists to develop a range of preparative strategies with easy scalability, improvement in efficiency, as well as reduction in cost/waste. Traditional methods to synthesize 1,4-benzoxazines involve multistep processes including cyclocondensation[8,14,19], epoxide opening[20,21] and metal catalyzed reaction.[22-24] In our continuing effort to develop novel diversified analogues, we directed our library construction based on the scaffold of tricyclo-1,4-benzoxazines. Although extensive studies have been carried out for the synthesis of benzoxazines, there are few reports on this scaffold. One similar report by Saito involved the reaction of 3-substituted indoles with singlet oxygen followed by catalytic HCI induced rearrangement of the resulting peroxidic intermediates.[25,26] We employed the starting material **1a**, the photocatalyst rose bengal, and MeOH. The mixture was vigorously stirred and irradiated with a tungsten-bromine lamp in the present of O_2 at -70 ^oC for 4 h. Treatment of the resulting hydroperoxide with catalytic amounts of HCI at room temperature provided **2a** in 43% yield. After many trials under this condition, we found that this procedure suffered from several disadvantages. Firstly, the reaction is limited in scope by the relatively low temperatures (-70 ^oC) and two steps required. Secondly, it is difficult to perform on gram scale and the reaction always needs longer reaction time, resulting in low yields. Thirdly, the application scope is limited, only few substrates could be performed under this condition. Thus, there is a demand for development of a more general and environment friendly procedure. Herein, we report our one-pot synthesis of tricyclo-1,4-benzoxazines via visible-light photoredox catalysis in continuous flow.

Results and discussion

According to our previous work on practical *N*-demethylation by using our upgraded home-made continuous-flow photoreactor[27] and Saito's procedure[25], we envisioned that mild conditions (one-pot synthesis), satisfactory yields and simple operation could be achieved. As rearrangement of the peroxidic intermediates might be induced by acid, we first selected **1a** as template substrate in the present of catalytic methylene blue (MB) and different acids under 34 W white LEDs light irradiation in continuous flow for the condition optimization (**Table 1**). Initial results revealed that among the most tested acid (Table 1, entries 2–8), good to excellent yields of **2a** were obtained, while the replacement of TsOH with AcOH or CH_3SO_3H afforded **2a** in low yields (entries 2 and 8). No desired product was detected if the acid was omitted (entry 1). Notably, in the absence of O_2, it resulted in a loss of reactivity (entries 9-10). This indicated that oxygen was crucial for the reaction to occur. Encouraged by these promising results, we next surveyed the amount of the acid under air atmosphere (entries 9, 11-12). Lowering the amount of TsOH to 0.5 or 0.1 equiv slightly decreased the yield to 91% or 73%, respectively (entries 11-12). Extensive efforts on the investigation of the molar ratios of alcohol used in the reaction were conducted. Disappointingly, when using CH_3CN as the solvent and lowering the amount of alcohol, the reaction requires a long time, resulting in unsatisfied yield (entries 13). This reaction also worked smoothly in the presence of $TsOH \cdot H_2O$ and air (entry 14), indicating that the presence of water has a minor influence on the cyclization of indole derivates. Further evaluation of the commercially available photoredox catalysts revealed that $Ru(bpy)_3Cl_2 \bullet 6H_2O$ can also provide the good yield (entry 15). The photoredox reaction was conducted in batch under the similar condition. As anticipated, complete conversion of the reaction

requires more than 24 h, in contrast to flow chemistry requiring only 1 h (entries 7, 16).

Table 1. Optimization of the reaction conditions.[a]



1a **2a**

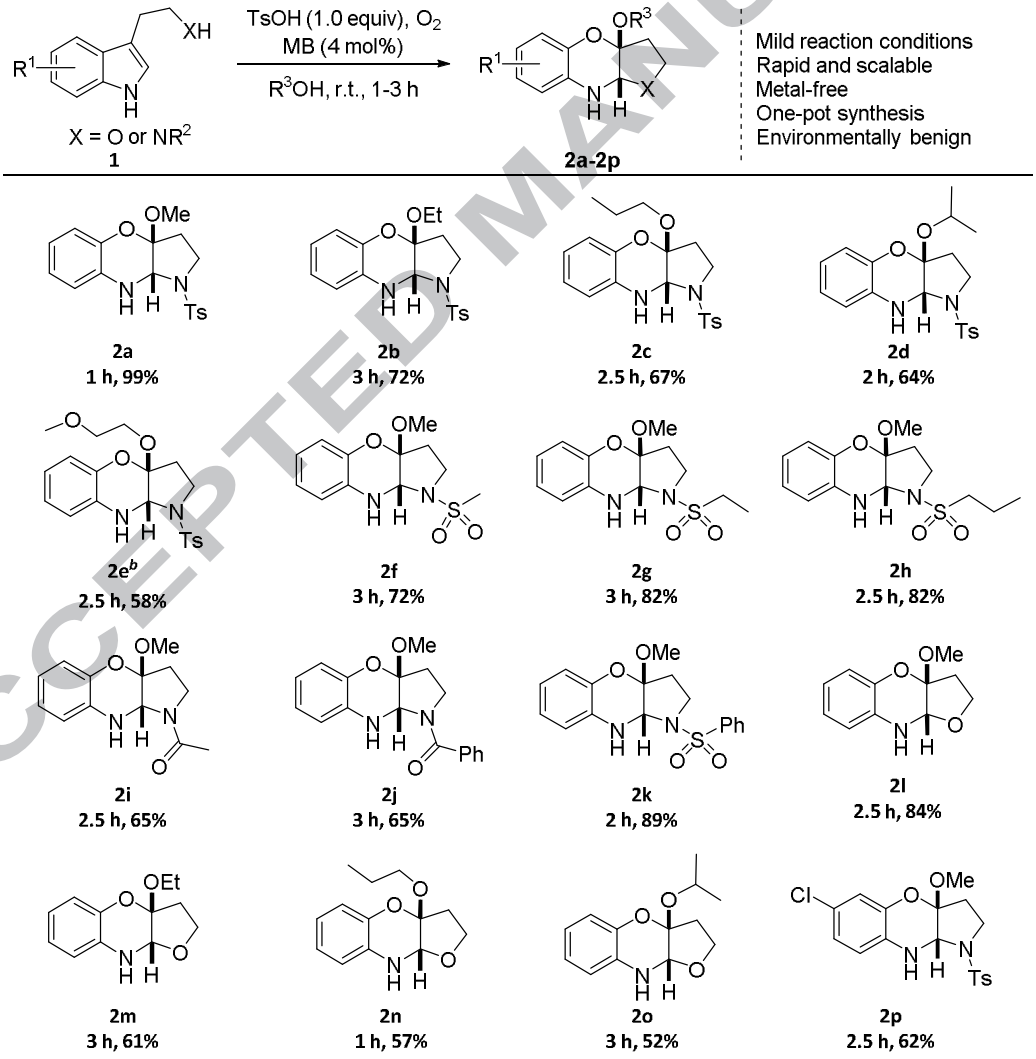
Entry	Acid (equiv.)	Atm.	Time (h)	Yield (%)[b]
1	0	O_2	5	trace
2	AcOH (1.0)	O_2	1	27
3	HCl (1.0)	O_2	1	91
4	H_2SO_4 (1.0)	O_2	1	94
5	HNO_3 (1.0)	O_2	1	87
6	CF_3CO_2H (1.0)	O_2	1	95
7	**TsOH (1.0)**	**O_2**	**1**	**99**
8	CH_3SO_3H (1.0)	O_2	4	60
9	TsOH (1.0)	Air	2	93
10	TsOH (1.0)	N_2	24	trace
11	TsOH (0.5)	Air	2	91
12	TsOH (0.1)	Air	2	73
13[c]	TsOH (1.0)	O_2	3	60
14	TsOH·H_2O (1.0)	O_2	1	98
15[d]	TsOH (1.0)	O_2	1	89
16[e]	TsOH (1.0)	O_2	24	73

[a]Reaction condition: **1a** (0.2 mmol), MB (4 mol%) in MeOH (25 mL), ambient temperature, irradiated with 34 W LEDs under a specific atmosphere. [b]Isolated yield unless otherwise noted. [c]Reaction was conducted in CH_3CN (25 mL) and MeOH (100.0 equiv). [d]$Ru(bpy)_3Cl_2$•$6H_2O$ as the photocatalyst. [e]Reaction was conducted in batch.

Having identified the optimal reaction conditions, we next set out to examine the scopes of photoredox catalysis synthesis of 1,4-benzoxazines. As shown in **Table 2**, a variety of alcohols as solvents were examined. The commonly used alcohols, such as methanol, ethanol and propanol, underwent the cyclization smoothly which provided the desired tricyclebenzoxazines in good yields (**2a**-**2d**). When the reaction was conducted in CH_3CN solvent and 2-methoxyethan-1-ol was used as the nucleophiles, gratifyingly, a moderate yield was observed (**2e**). In addition, the substrate scope of

N-monosubstituted tryptamines was explored. Typical *N*-protecting groups (R^2 = Ts, SO_2R, COR) on the side chain of tryptamine were all well tolerated, providing the desired tricyclo-1,4-benzoxazines in good yields (**2f**-**2g**). Furthermore, reactions of tryptophol or other tryptamines with varied alcohols were proceeded smoothly (**2l**-**2p**). Notably, gram-scale reaction of **1a** was also performed to evaluate the practicality of this photoredox reaction. As showed in **Figure 2**, the corresponding product **2a** was obtained in 78%. The chemical structure of **2a** was further confirmed by X-ray analysis.[28]

Table 2. Substrate scope of tricyclo-2,3-dihydro-1,4-benzoxazines.[a]



[a]Unless otherwise noted, the reaction condition was as followed: indole **1** (0.2 mmol),

MB (1.0 mmol%), TsOH (0.2 mmol), R^3OH (25 mL), 34 W LED light source, O_2, 1-3 h. Yield of isolated product. **2a-2e** were synthesized from the starting material **1a**, **2f** from **1b**, **2g** from **1c**, **2h** from **1d**, **2i** from **1e**, **2j** from **1f**, **2k** from **1g**, **2l-2o** from tryptophol, **2p** from **1h**. See the Supporting Information for more details. [b] CH_3CN as the solvent and 2-methoxyethanol (10 mmol).

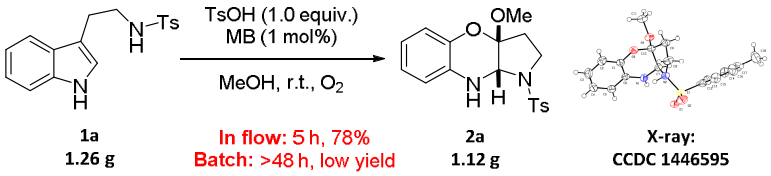


Figure 2. The gram-scale reaction.

The proposed mechanism was depicted in **Figure 3**. First, methylene blue (MB) is excited under visible light irradiation to produce its excited state species $[MB^+]$*, which interacts with **A** to generate cation radical **B** via the electron transfer.[29] In this process, the excited state $[MB^+]$* turns to the semireduced form MB•. The radical intermediate **B** readily undergoes intramolecular cyclization to give tricyclo-indole radical **C**. The radical MB• transfers an electron to oxygen to produce superoxide $O_2•^-$ and MB• returns to its ground state.[30] Subsequently, the generated $O_2•^-$ reacts with the tricyclo-indole radical **C** to yield hydroperoxide **D**. In the presence of acid, the terminal hydroperoxy oxygen atom is protonated followed by phenyl group migration from the benzyl carbon to the adjacent oxygen, producing a resonance stabilized tertiary carbocation **E.** The tricycle-benzoxazine cation can be trapped by the *O*-nucleophile, furnishing exclusively the desired product.

Conclusion

In conclusion, a practical method for the cyclization of indole derivatives via visible-light photoredox catalysis in continuous flow has been developed. To the best of our knowledge, there is little information available in literature about the

cyclization of tryptamine via visible-light photoredox catalysis in flow. This reaction can be run in one-pot fashion, and does not require expensive metal-free catalysts, providing a focused compound library in good yields within remarkably short time.

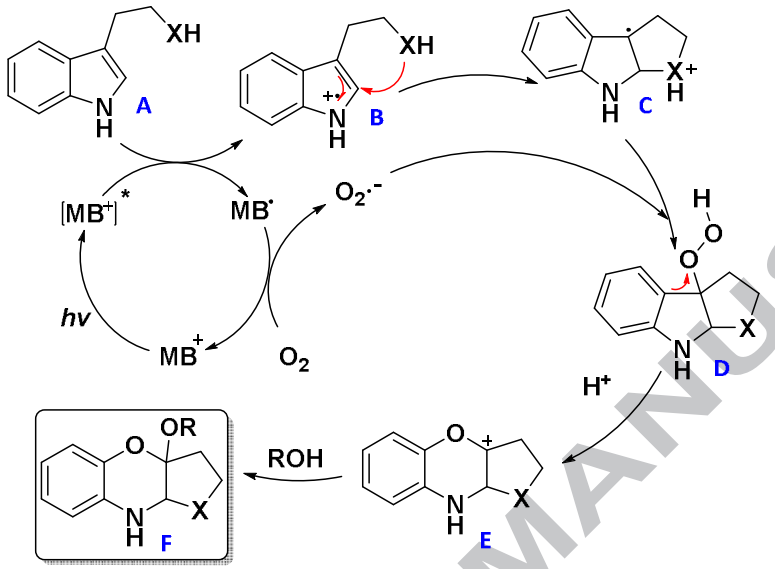


Figure 3. Proposed Mechanism.

Experimental section

General Information. All reactions were performed under a designated atmosphere in flame-dried round bottom flasks, magnetically stirred. Preparative column chromatography was performed using silica gel 60, particle size 0.063–0.200 mm (70–230 mesh, flash). Analytical TLC was carried out employing silica gel 60 F254 plates (Merck, Darmstadt). Visualization of the developed chromatograms was performed with detection by UV (254 nm and 365 nm). Proton Nuclear Magnetic Resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker-400 (^{1}H, 400 MHz; ^{13}C, 101 MHz) spectrometer. Chemical shifts for protons are reported in parts per million and are references to the

NMR solvent peak ($CDCl_3$: δ 7.26). Chemical shifts for carbons are reported in parts per million and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ 77.16). Signals are listed in ppm, and multiplicity identified as s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet. Chemical shifts were expressed in ppm, and *J* values were given in Hz. High resolution mass spectra (HRMS) were obtained from Thermo Fisher Scientific Exactive Plus mass spectrometer. Melting point was determined using the X-4A melting point apparatus (Shanghai Yidian Co., Ltd.) and uncorrected. Purified compounds were further dried under high vacuum (0.01–0.10 Torr). Yields refer to purified and spectroscopically pure compounds, unless otherwise noted. All commercially available starting materials and solvents were reagent grade, and used without further purification.

General procedure for the reaction in continuous flow. A 100 mL round bottom flask equipped with a magnetic stir bar was charged with **1** (0.2 mmol), TsOH (0.2 mmol) and catalytic amount of MB. The corresponding alcohol (25 mL) was added. The resulting blue solution was sucked into the Home-Made Continuous-Flow Photoreactor at one end and returned at the other (rpm = 50, flow rate is ~10 mL/min). The flow reaction was conducted under O_2 in the home-made capillary photoreactor with a LongerPump (Pump model: YZ1515x). Two 20 mL Reaction Towers were in series connection, each with a LED corn light bulb (34 W) in the center. Relatively mild heating (< 30 °C) of the reaction mixture was observed after a long period of time. The flow reaction was completed in 1-3 h. After completion of the reaction by TLC analysis, the mixture was collected and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give **2** (52-99% yields).

(3aR,9aS)-3a-methoxy-1-tosyl-1,2,3,3a,9,9a-hexahydrobenzo[b]pyrrolo[2,3-e][1,4]Oxazine (2a). To a solution of **1a** (63 mg, 0.2 mmol) in MeOH (20 mL) was

added TsOH (34 mg, 0.2 mmol) and MB (3 mg, 4 mol%). The resulting solution was then irradiated by a LED strip and stirred for 1 h in continuous flow. The reaction mixture was removed from the light source and concentrated to give crude product under reduced pressure. The residue was purified by silica gel chromatography (PE/EtOAc = 2:1) to give the target product as a white solid (71 mg, 99%). Physical State: white solid; Melting Point: 181.2-182.7 ^{o}C; TLC: R_f = 0.36 (PE/EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.91 – 6.79 (m, 2H), 6.76 – 6.69 (m, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.02 (s, 1H), 4.97 (d, *J* = 3.2 Hz, 1H), 3.50 – 3.40 (m, 2H), 3.36 (s, 3H), 2.40 (s, 3H), 2.36 – 2.30 (m, 1H), 1.82 – 1.71 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.87, 140.48, 135.12, 129.87, 129.17, 127.41, 122.77, 119.48, 116.89, 115.06, 101.12, 70.41, 51.39, 44.21, 32.02, 21.58; HRMS (ESI): calcd for $C_{18}H_{20}N_2O_4S$ $[M + H]^+$ *m/z* 361.1217, found 361.1221.

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Notes

The authors declare no competing financial interest.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Nos. 81402781 and 81571802), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, Natural Science Foundation of Fujian Province (2016J06020).

Supplementary data

Supplementary data (Characterization data, copies of ^{1}H and ^{13}C NMR spectra of all synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/xxx.

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Highlights

- A facile continuous-flow method to access tricyclo-1,4-benzoxazines.
- The reaction was efficiently achieved at ambient temperature.
- The procedure could be easily handled and scaled up.
- Enabling construction of a focused compound library.