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Visible light-promoted metal-free intramolecular cross dehydrogenative coupling approach to 1,3-oxazines

Paran J. Borpatra, Mohit L. Deb *, Pranjal K. Baruah *

Department of Applied Sciences, GUIST, Gauhati University, Guwahati 781014, Assam, India

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ABSTRACT

Visible light promoted intramolecular cross dehydrogenative coupling of 1-aminoalkyl-2-naphthols to 1,3-oxazines is developed. Green LED lamp was used as the light source and eosin Y functions as photoredox catalyst. The reaction was carried out in the absence of transition-metal photoredox catalysts and additional additives. Aerial oxygen was used as the terminal oxidant. The method offers clean and efficient synthesis of these important classes of heterocycles.

Introduction

Cross dehydrogenative coupling (CDC) is the centre of current research as it provide step- and atom-economical strategy for the synthesis of complex organic compounds from simple molecules through C–H functionalization.[1] In addition, it is more environment-friendly than cross-coupling reactions which require prefunctionalization of substrates.[1] The direct functionalization of unactivated sp^3 C–H bonds α- to tertiary amine leading to C-heteroatom bonds has attracted much more attention in the field of heterocycle synthesis.[2] Among various C–X bonds, the formation of C–O bond has more or less studied.[3] However, all the methods used transition metal/non-metal catalyst along with an oxidant. As most of the metal catalysts are expensive and toxic, therefore, performing the reaction without using metal catalysts and oxidants are in limelight. Bronsted acid was also used to catalyze this type of CDC reactions in presence of an oxidant.[4]

Recently, visible light photoredox catalysis have found many applications in organic synthesis as it allows chemists to exploit the synthetic potential of single-electron-transfer (SET) processes.[5] Among various transformations, the oxidation of tertiary amines to highly reactive iminium ions followed by functionalizations has been well studied.[6] Unlike thermal reactions, photoredox catalysis occur under mild conditions and does not require radical initiators or stoichiometric chemical oxidants/reductants. Moreover, light is an inexpensive, abundant, non-polluting, and renewable reagent for chemist. Ruthenium and iridium complexes are usually employed for the visible light photo catalysis.[7] However, due to expensive and toxic nature, their application in large scale has been prevented. As an alternative to transition metal complexes in photocatalysis, organic dyes have recently been used as they are non-toxic and much cheaper.[8] For instance, eosin Y and Rose bengal were widely used as an organo-photocatalyst in synthetic chemistry.[9]

Since tetrahydroisoquinoline (THIQ) derivatives are very much known for their bioactivity (Fig. 1),[10] we planned to synthesize 1,3-oxazines having THIQ moiety. 1,3-Oxazines display wide spectrum of biological activities, such as anti-HIV, antibacterial, antitumor, antituberculosis, and fungicidal.[11] For example, PD-102,807 acts as a selective antagonist for the muscarinic acetylcholine receptor M_4.[10a,b] CX-614 is an ampakine drug which is investigated for its effect on AMPA receptors.[12] Dolutegravir is used to treat HIV infection.[13] Furthermore, few 1,3-naphthoxazine derivatives are used for the treatment of Parkinson's disease and are also applied as potent non-steroidal progesterone receptor agonists.[14] Hence, a number of techniques have been developed for their synthesis.[15]

However, their synthesis by using cyclic amines is inadequate. Maycock et al. first reported the synthesis of such 1,3-oxazines by using Cu (II) salt[16] and later, our group published the synthesis of same by using I_2 catalyst.[17] Chandrasekharam and co-workers recently synthesized such compounds by using three-component

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* Corresponding authors.

E-mail addresses: mohitdd.deb@gmail.com (M.L. Deb), baruah.pranjal@gmail.com (P.K. Baruah).

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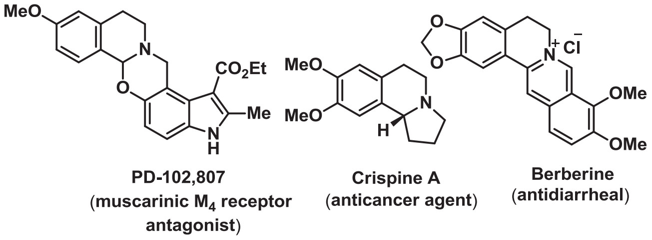
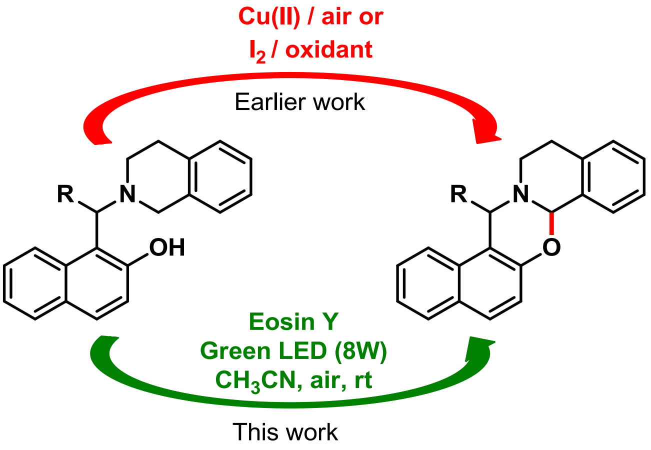


Fig. 1. Bioactive THIQ derivatives.



Scheme 1. Synthesis of 1,3-oxazines *via* CDC.

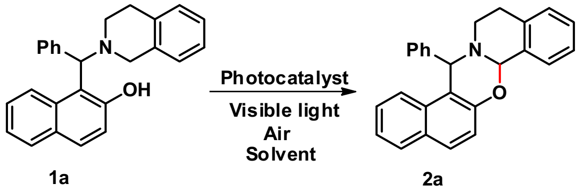
protocol catalyzed by CuI/molecular sieve under N_2 atmosphere.[18] However, all these synthetic methods either involve metal/non-metal catalyst in hazardous solvents or stoichiometric oxidant. Intermolecular photoredox aided functionalization of sp^3 C–H bonds adjacent to the nitrogen atom in tetrahydroisoquinoline were earlier studied.[9b,19] However, intramolecular photoredox catalyzed C–H functionalization is scarce.[20] In continuation of our ongoing work on oxidative generation of reactive iminium intermediates,[17,21] here we report visible light-promoted construction of 1,3-oxazines from 1-aminoalkyl-2-naphthols[22] through a photocatalytic C–H functionalization using eosin Y as photoredox catalyst (Scheme 1).[23]

Results and discussions

We started our study with the optimization for the synthesis of **2a** from **1a** and the results are presented in Table 1. We found that eosin Y as photoredox catalyst under the irradiation of green LED in acetonitrile solvent at room temperature offered the highest yield (entry 6, Table 1). We tested other solvents like EtOH, H_2O, DMF, and toluene; however, no one showed promising result (entries 2–5, Table 1). Increasing catalyst loading did not increase the yield, while decrease of the same decreased the product yield (entries 8–9, Table 1). Use of blue LED as the light source gave us moderate yield, whereas CFL offered poor yield of **2a** (entries 11–12, Table 1). In presence of Rose Bengal, another organic photoredox catalyst, the reaction furnished 63% of **2a**, whereas methylene blue did not respond to this reaction (entry 13–14, Table 1).

Having identified the optimized reaction conditions, we next explored the scope of 1-aminoalkyl-2-naphthols **1**. We observed that electron-withdrawing groups present in the phenyl ring of R

Table 1
Optimization of the reaction.[a]



Entry	Photocatalyst (mol%)	Solvent	Time (h)	Yield (%)
1	Eosin Y (2)	–	12	–
2	Eosin Y (2)	EtOH	12	10
3	Eosin Y (2)	DMF	12	–
4	Eosin Y (2)	Toluene	12	22
5	Eosin Y (2)	H_2O	12	–
6	**Eosin Y (2)**	**CH_3CN**	**10**	**72**
7	Eosin Y (2)	CH_3CN	12	72
8	–	CH_3CN	10	–
9	Eosin Y (3)	CH_3CN	10	71
10	Eosin Y (1)	CH_3CN	10	40
11[b]	Eosin Y (2)	CH_3CN	12	57
12[c]	Eosin Y (2)	CH_3CN	12	14
13	Rose Bengal (2)	CH_3CN	12	63
14	Methylene blue (2)	CH_3CN	12	–

[a] Unless otherwise mentioned, all the reactions were performed by using **1a** (0.5 mmol, 183 mg) under open air and photoirradiation with 8 W green LED ($\lambda \approx 530$ nm). Products were purified by column chromatography and yields are for the isolated products.
[b] Reaction was carried out with 8 W blue LED.
[c] Reaction was carried out with 20 W CFL.