Eosin Y-catalyzed visible-light-mediated aerobic oxidative cyclization of N,N-dimethylanilines with maleimides
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Abstract
A novel and simple strategy for the efficient synthesis of the corresponding tetrahydroquinolines from N,N-dimethylanilines and maleimides using visible light in an air atmosphere in the presence of Eosin Y as a photocatalyst has been developed. The metal-free protocol involves aerobic oxidative cyclization via sp³ C–H functionalization process to afford good yields in a one-pot procedure under mild conditions.

Introduction
Over the past several years, visible light photoredox catalysis has become a powerful and promising tool and has been productively used to drive chemical transformations in the field of organic synthesis [1-6]. The approach takes full advantage of visible light, which is clean, abundant, and renewable. The pioneering work in this research area, reported by the groups of MacMillan [7-9], Yoon [10,11], Stephenson [12,13] and others [14-18], has demonstrated that ruthenium and iridium complexes as visible light photoredox catalysts are capable of catalyzing a broad range of useful reactions. A variety of new methods have been developed to accomplish known and new chemical transformations by means of these transition metal-based photocatalysts so far.

However, the ruthenium and iridium catalysts usually are high-cost, potentially toxic and not sustainable. Similar to the redox properties of these organometallic complexes, some metal-free organic dyes such as Eosin Y, Rose Bengal, Fluorescein, and Methylene Blue, have shown superiority of their applications as photocatalysts, which are easy to handle, environmentally friendly, inexpensive, and have great potential for applications in visible-light-mediated photoredox reactions [19-27].

More recently, visible-light-induced sp³ C–H bond functionalization adjacent to nitrogen atoms has been extensively studied and has become a fundamental organic transformation [28-38]. Tertiary amine A generally generates a nucleophilic α-amoно-
alkyl radical B or an electrophilic iminium ion C via visible-light photoredox catalysis. Unfortunately the research of the α-aminoalkyl radical is limited in photochemical synthesis because it tends to form the iminium ion by one electron oxidation (Scheme 1) [39-41].

Scheme 1: Visible-light-induced sp\(^3\) C–H bond functionalization of tertiary amines.

In the context of this research background, we investigated the α-aminoalkyl radical route to achieve the aerobic oxidative cyclization of N,N-dimethylanilines with maleimides to form the corresponding tetrahydroquinoline derivatives under organic dye Eosin Y catalysis. Swan and Roy reported the reaction using benzoyl peroxide as catalyst at low temperature as early as 1968 [42]. In 2011, Miura and co-workers achieved this transformation using a copper catalyst and air as the terminal oxidant [43]. Bian and co-workers presented the same reaction using [Ru(bpy)]\(^3+\) as photoredox catalyst under irradiation with visible light next year [44]. Herein, we show an environmentally friendly aerobic oxidative cyclization methodology that avoids the use of metal catalysts and makes full use of air as oxidant.

Results and Discussion

Our investigations for the envisaged protocol commenced with the reaction of N,N-dimethylaniline (1a) (0.5 mmol) with N-phenylmaleimide (2a) (0.25 mmol) in MeCN (3 mL) in the presence of 3 mol % Eosin Y under an air atmosphere at rt. Isolated yield of the product 3a: n.r., = no reaction.

Next, we optimized the reaction conditions with respect to solvent and catalyst dosage. MeCN was found to be the best solvent (Table 2, entry 1) among DMF, DCE, DCM, DMSO, acetone, dioxane, and MeNO\(_2\). When the amount of Eosin Y was decreased from 3 mol % to 2 mol % or increased from 3 mol % to 4 mol %, the yield of the tetrahydroquinoline product 3a was slightly reduced (Table 2, entries 9 and 10). Thus, the optimum catalyst dosage of Eosin Y was found to be 3 mol %.

With the optimized conditions in hand, the substrate scope of this reaction was examined (Scheme 2). The reaction is mild and tolerates many functional groups. N,N-dimethylaniline and substituted N,N-dimethylanilines incorporating methyl and bromo on the phenyl ring reacted with 2 to afford the corresponding tetrahydroquinolines 3 in good yields. N-arylmaleimides with electron-donating groups such as methyl, methoxy

Table 1: Screening and control experiments\(^a\).

| Entry | Organic dye | Oxidant | Yield (%)\(^b\) |
|-------|-------------|---------|---------------|
| 1     | Eosin Y     | air     | 82            |
| 2     | Rose Bengal | air     | 67            |
| 3     | Methylene Blue | air | trace        |
| 4     | Fluorescein  | air     | trace        |
| 5     | Eosin Y     | O\(_2\)\(^c\) | 77            |
| 6     | Eosin Y     | air     | 69\(^d\)      |
| 7     | Eosin Y     | air     | 73\(^e\)      |
| 8     | none        | air     | n.r.          |
| 9     | Eosin Y     | air     | n.r.          |
| 10    | Eosin Y     | none    | trace\(^g\)   |

\(^a\)Reaction conditions: 1a (0.5 mmol), 2a (0.25 mmol), organic dye (3 mol %), MeCN (3 mL), two 9 W Blue LEDs irradiation under an air atmosphere at rt. \(^b\)Isolated yield of the product 3a; n.r., = no reaction. \(^c\)Under O\(_2\) (1 atm, balloon). \(^d\)0.25 mmol of 1a and 0.25 mmol of 2a were used. \(^e\)0.25 mmol of 1a and 0.5 mmol of 2a were used. \(^f\)The reaction was carried out in the dark. \(^g\)Under N\(_2\).
Scheme 2: Substrate scope for aerobic oxidative cyclization of N,N-dimethylanilines with maleimides.
and electron-withdrawing groups such as chloro, bromo, and \(N\)-methylmaleimide all underwent the aerobic oxidative cyclization to give the corresponding products in good yields. When using 4,4'-methylenbis(\(N\),\(N\)-dimethylaniline) as the substrate, the reaction occurred only on one side and the yield of the product 3p is 52%. The reaction of \(X\),\(N\),3-trimethylaniline and \(N\)-phenylmaleimide resulted in the formation of a mixture of regioisomers 3q1 and 3q2 with 81% combined yield. The major product was the sterically more hindered 3q1 [43-45].

On the basis of our observations and literature reported [19,36,38,43,44], a proposed mechanism for the formation of the corresponding tetrahydroquinolines 3 form \(N\),\(N\)-dimethylanilines 1 and maleimides 2 is depicted in Scheme 3. On absorption of visible light, the ground state of Eosin Y (EY) is induced to its single excited state (\(1^\text{EY}^*\)), which moves to its more stable triplet excited state (\(3^\text{EY}^*\)) through inter system crossing (ISC) [46,47]. \(3^\text{EY}^*\) may undergo an oxidative or reductive quenching cycle [48-50]. In this mechanism, a single electron transfer (SET) from 1 to \(3^\text{EY}^*\) generates the amine radical cation 4, and at the same time, \(3^\text{EY}^*\) is reduced to the EY\(+\). In the presence of oxygen, the photoredox catalytic cycle of EY is finished via a SET oxidation, with the production of a superoxide radical anion \(O_2^\text{−}\). Deprotonation of 4 generates

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**Table 2: Optimization of reaction conditions\(^a\).**

| Entry | Eosin Y (mol %) | Solvent | Yield (%)\(^b\) |
|-------|----------------|---------|-----------------|
| 1     | 3              | MeCN    | 82              |
| 2     | 3              | DMF     | 47              |
| 3     | 3              | DCE     | 71              |
| 4     | 3              | DCM     | 37              |
| 5     | 3              | DMSO    | trace           |
| 6     | 3              | acetone | 64              |
| 7     | 3              | dioxane | 51              |
| 8     | 3              | MeNO\(_2\) | 58          |
| 9     | 2              | MeCN    | 80              |
| 10    | 4              | MeCN    | 77              |

\(^a\)Reaction conditions: 1a (0.5 mmol), 2a (0.25 mmol), solvent (3 mL), two 9 W blue LEDs irradiation under an air atmosphere at rt. \(^b\)Isolated yield of the product 3a.

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**Scheme 3: A proposed reaction mechanism.**
α-aminoalkyl radical 5. Then 5 reacts with 2 to generate radical 6, and the latter then undergoes cyclization to form intermediate 7. Proton and electron transfer from 7 to $O_2^{-}$ yields the final product 3 and HOO$^-$. The HOO$^-$ will be subsequently protonated to yield $H_2O_2$ as the by-product. $H_2O_2$ was detected after the reaction was completed by using KI/starch indicator (see the Supporting Information File 1). The involvement of radical pathway was supported by experimental result that the reaction was suppressed in the presence of TEMPO.

Conclusion

In conclusion, we report an efficient metal-free method for the synthesis of corresponding tetrahydroquinolines from $N,N$-dimethylanilines and maleimides using molecular oxygen as the greenest reagents, light. The protocol is significantly green because it utilizes oxidant and Eosin Y as catalyst under the irradiation of visible light. The protocol is significantly green because it utilizes visible light and atmospheric oxygen as the greenest reagents, and metal-free, cheap Eosin Y with a relatively low loading as the photocatalyst to deliver the product at room temperature in a simple one-pot procedure. This methodology expands the range of substrates in the area of visible light photoredox reactions.

Supporting Information

Supporting Information File 1

Experimental section and characterization of the synthesized compounds.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-48-S1.pdf]

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