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Photocatalytic aerobic oxidation/semipinacol rearrangement sequence: a concise route to the core of pseudoindoxyl alkaloids

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Pseudoindoxyl alkaloids featuring the 2,2-disubstituted indolin-3-one core structure constitute an important family of indole alkaloids.¹ For example, (+)-Aristotelone, Brevianamide A, and Duocarmycin C_1/B_1 are some of the representative natural isolates with diverse biological activities (Fig. 1).^{1b-d} Not surprisingly, a great deal of efforts has been devoted to the construction of these core structures.² In this context, the protocol of oxidation of indoles to indol-3-ols followed with a semipinacol rearrangement³ represents one of the most powerful routes to 2,2-disubstituted indolin-3-ones (Scheme 1, A).^{2b,d,g} However, this methodology suffered from some limitations, including stepwise operation, involvement of strong or not atom-economic oxidants (i.e. Oxone, HNO_2 , H_2O_2 , et al.)^{2b,g,m} for the oxidative step and the requirement of acidic, basic, or heating conditions^{2a,c,e,f} for the following rearrangement process. Thus, the search for more straightforward methods with the use of 'green oxidant' to directly convert 2,3disubstituted indoles into the corresponding 2,2-disubstituted indolin-3-ones still remains highly desirable.

Over the past decade, molecular oxygen has been widely utilized as an ideal terminal oxidant for oxidation reactions because of its environmentally friendly and low-cost advantages.⁴ Recently, photocatalytic aerobic oxidation under mild reaction condition has received increasing attention as a result of its inherent features of green chemistry and sustainability.⁵ In these

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ABSTRACT

A visible light-induced photocatalytic aerobic oxidation/semipinacol rearrangement has been successfully developed. This methodology allows for efficient conversion of a wide range of indoles into the synthetically significant 2,2-disubstituted indolin-3-ones, the core structure of pseudoindoxyl alkaloids, under mild reaction conditions.

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Figure 1. Representative examples of pseudoindoxyl alkaloids.

reactions, molecular oxygen is used not only as an oxidizing agent to accomplish the photoredox catalytic cycle but also as a terminal oxygen source introduced into products.⁶ For example, in 2003, Zen and co-workers disclosed a highly selective oxidation reaction of sulfide to sulfoxide using O₂ under the visible light-induced photoredox reaction conditions.^{6a} In 2011, the Jiao group has realized an efficient oxidative transformation of aryl halides to aryl carbonyl compounds using air as the oxidant, by merging photocatalysis and organocatalysis.^{6b} Shortly after, Xia and co-workers described a visible light promoted aerobic oxidative C—C bond cleavage of aldehvdes to prepare a series of ketones with good yields.^{6e}

Recently, our group developed an aerobic oxidation/[3+2] cycloaddition/oxidative aromatization sequence via visible light photocatalysis.⁷ As a thematic extension, we proposed that this visible light induced oxidation could be served as an important platform for the construction of pseudoindoxyl core via photocatalytic aerobic oxidation/semipinacol rearrangement sequence (Scheme 1, B). Herein, we disclose the successful implementation of this idea,

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Scheme 1. Construction of 2,2-disubstituted indolin-3-ones via semipinacol rearrangement.

and document a new step-, atom- and redox-economic⁸ methodology, that can be used for the preparation of a wide range of 2,2-disubstituted indolin-3-ones.

Initially, the feasibility of the proposed reaction was examined by using 3-benzyl-2-phenyl indole **1a** as the model substrate in the presence of 5 mol % of $Ir(ppy)_2(dtb-bpy)PF_6$ under 3W white LED irradiation. To our delight, the reaction indeed proceeded smoothly in CHCl₃ and afforded the desired product **2a** in 64% yield (Table 1, entry 1). Encouraged by this result, we continued to optimize the condition by varying reaction parameters. It was found that solvents had a dramatic impact on the reaction, and CHCl₃ was identified as the best solvent of choice (entries 1-6). Subsequently, a series of iridium, ruthenium, and dye photocatalysts were screened to further improve the reaction efficiency (entries 7–12). It turned out that the yield could be improved to 69% when we applied $Ru(bpy)_3Cl_2 \cdot 6H_2O$ as a photocatalyst, albeit with a longer reaction time (entry 9). Notably, when the catalyst loading was decreased to 3 mol %, the reaction could give the best result (entry 13, 74% yield). Significantly, the direct application of air as oxygen source also proved to be suitable for the reaction, while a slight decrease in yield (entry 14, 56% yield) was observed. Finally, control experiments confirmed that photocatalyst, visible light, and oxygen were all critical for this process.⁹

With the optimal reaction conditions in hand, we then investigated the substrate scope of this sequential photocatalytic aerobic oxidation and semipinacol rearrangement. As illustrated in Table 2, a variety of structurally diverse 2-phenyl-3-benzyl indoles were able to undergo this reaction smoothly. As for the effect of electronic properties of the substituents on the phenyl ring, the electro-rich substrates (1b and 1c) showed slightly higher reactivity than electro-deficient one (1d). Importantly, the phenol group (1e), which can be easily oxidized to quinone, was also well tolerated under the present oxidative condition, affording the desired product in a moderate yield (2e: 45% yield). In addition, the naphthyl (1f) and heteroaryl (1g) substituted substrates participated in the reaction well to give the corresponding products **2f** and **2g** in 47% and 51% yield, respectively. Notably, several indoles with alkyl groups at 3-position, such as cyclohexyl (1h), iso-butyl (1i), and allyl (1i), were also easily transformed into the corresponding products **2h-2i** in moderate to good vields.

In addition to the phenyl group, variation of aryl substituents on the 2-position of indole substrates were also successfully achieved. As highlighted in Table 3, all these substrates can be transformed into the corresponding products (**2k**-**n**) with moderate to excellent yields. For example, highest isolated yield (94%) was obtained in the case of substrate **11** with a methoxyl group on phenyl ring, probably due to the higher susceptivity to the single electron oxidation by the excited photocatalyst (please see the mechanism analysis in Scheme 2). Moreover, we found that indole **10** with a thienyl at 2-position was well compatible with the reaction conditions and furnished the desired product **20** in 78% yield.

Finally, we turned our attention to the diversity of the benzene ring of indole. As shown in Table 4, variation of the substation pattern has no deleterious effect on the reaction efficiency (**2p**, **2q**: 76%). Besides, various indoles bearing electron-rich (MeO) and - deficient (F, Br) substituents at 5-position can react well to furnish the desired products **2r**-**2t** in moderate to good yields (52–84%). The structure of representative product **2t** was further confirmed by X-ray crystallographic analysis.¹⁰

Importantly, a gram scale reaction with **1a** (4 mmol, 1.13 g) has been carried out to prove the practicability of this sequential process, providing the desired product **2a** in 71% yield without affecting the efficiency (Eq. (1)). More significantly, this sequential photocatalytic aerobic oxidation/semipinacol rearrangement

Table 1

Optimization of reaction conditions^a



Entry	Photocatalyst	Solvent	Time (h)	Conversion ^b (%)	Yield ^b (%)
1	Ir(ppy) ₂ (dtb-bbpy)PF ₆	CHCl ₃	48	96	64
2	Ir(ppy) ₂ (dtb-bbpy)PF ₆	CH ₂ Cl ₂	40	95	29
3	Ir(ppy) ₂ (dtb-bbpy)PF ₆	DCE	48	56	32
4	Ir(ppy) ₂ (dtb-bbpy)PF ₆	CH₃CN	25	97	20
5	$Ir(ppy)_2(dtb-bbpy)PF_6$	DMF	25	90	17
6	$Ir(ppy)_2(dtb-bbpy)PF_6$	DMSO	16	>99	18
7	$Ir(ppy)_2(bpy)PF_6$	CHCl ₃	48	97	60
8	Ir(ppy) ₃	CHCl ₃	48	97	33
9	Ru(bpy) ₃ Cl ₂ ·6H ₂ O	CHCl ₃	72	90	69
10	$Ru(bpy)_3(PF_6)_2$	CHCl ₃	96	80	56
11	$Ru(bpm)_3(BArF)_2$	CHCl ₃	48	93	44
12	Eosin Y	CHCl ₃	48	99	61
13 ^c	Ru(bpy) ₃ Cl ₂ ·6H ₂ O	CHCl ₃	72	95	74(76) ^d
14 ^{c,e}	$Ru(bpy)_3Cl_2\cdot 6H_2O$	CHCl ₃	72	81	56

^a Unless otherwise noted, the reaction was carried out with **1a** (0.3 mmol), photocatalyst (5 mol %) in the solvent (3.0 mL) at 30 °C under 3W white LED irradiation. ^b Determined by GC.

^cUsing 3 mol % of photocatalyst.

^dIsolated yield in parentheses.

^ePerformed under an air atmosphere.

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Table 2

Variation of the substituents on the 3-position of indoles^a



 $[^]a$ Unless otherwise noted, the reaction was carried out with 1 (0.3 mmol), $Ru(bpy)_{3-}$ Cl₂·6H₂O (3 mol %) in CHCl₃ (3.0 mL) at 30 °C under 3W white LED irradiation; isolated yield.

^bUsing 5 mol % of Ir(ppy)₂(dtb-bbpy)PF₆.

Table 3

Variation of the substituents on the 2-position of indoles^a







Scheme 2. Proposed mechanism.

reaction showed promising synthetic potential in one-step construction of the spirocyclic indolin-3-one product **2u**, the intrinsic core of (+)-Aristotelone and Brevianamide A, albeit with a comparatively low yield (Eq. (2)). Further condition optimization for preparation of spirocyclic indolin-3-ones is still under active investigation.

To gain some insight into the possible mechanism, several control experiments were designed and executed. Firstly, the fluorescence quenching experiments with $Ru(bpy)_3Cl_2-6H_2O$ and cyclic voltammetry (CV) measurements of model substrate **1a** were performed. The results indicated that substrate **1a** (-0.04 V (vs SCE)) could be successfully oxidized by the photoexcited state $Ru(bpy)_3^{2+*}$ (+0.77 V (vs SCE)).⁹ Secondly, two ¹⁸O-labeling experiments by using ¹⁸O₂ and H₂¹⁸O were implemented (Eqs. (3) and (4)), and these results showed that the oxygen atom of

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Table 4

Variation of the substituent on the benzene ring of indole substrates^a



^a Unless otherwise noted, the reaction was carried out with **1** (0.3 mmol), Ru(bpy)₃₋ $Cl_2 \cdot 6H_2O$ (3 mol %) in CHCl₃ (3 mL) at 30 °C under 3W white LED irradiation; isolated yield.







the carbonyl group in the product originated exclusively from molecular oxygen rather than water.⁹ Moreover, we have also carried out a series of control experiments to investigate the possible intermediates. As shown in Eq. (5), the model reaction of **1a** could afford the 3-benzyl-2-phenyl-3*H*-indolin-3-ol **3a** in 17% isolated yield upon quenching after 6 h. Notably, when the isolated tertiary alcohol **3a** was re-treated under the standard conditions, it was exclusively converted into product **2a** in 90% yield after 24 h.



More remarkably, the variation process of starting material **1a**, transient species **3a**, and final product **2a** can be recorded through ¹H NMR analysis (Fig. 2). All these results suggested that the



Figure 2. Reaction profile of photocatalytic aerobic oxidation/semipinacol rearrangement sequence analyzed by ¹H NMR.

present sequential reaction most probably proceeded through the formation of key tertiary alcohol **3a**, an important precursor for the product **2a** via semipinacol rearrangement.

According to these experimental results, a plausible mechanism was proposed. As illustrated in Scheme 2, indole substrate **1** was oxidized to cation radical **I** by the photoexcited Ru(II)* through a reductive quenching process. The resultant Ru(I) was oxidized by the oxygen to regenerate Ru(II) with the formation of superoxide radical anion, which could react with **I** to give the intermediate **II** or **III**.^{6f,h} The following proton transfer and O—O cleavage processes would afford the tertiary alcohol **3**.^{6h,11} Finally, the formation of product **2** occurs via the chemospecific semipinacol rearrangement of the key intermediate **3** (R¹ migration).^{2e,3a} Note that, although the possibility of singlet oxygen-mediated process cannot be completely excluded at the current stage,¹² the results of the singlet oxygen quenching experiment indicated that it was not the predominating pathway for product formation.⁹

Preliminary studies have also revealed that the use of chiral phosphoric acid **4** as organocatalyst can induce the oxidation rearrangement reaction with promising levels of enantioselectivity (Eq. (7), 83% yield, 60% ee).¹³ Further to improve the enantioselectivity of this process is still ongoing in our laboratory.

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In conclusion, a highly efficient sequential photocatalytic aerobic oxidation/semipinacol rearrangement reaction has been accomplished in our laboratory. This reaction can transform a wide range of readily available indoles into synthetically significant 2,2disubstituted indol-3-ones in generally good yields under mild reaction conditions. Moreover, a plausible mechanism for this reaction was proposed based on ¹⁸O labeling experiments, luminescence quenching experiments, and the detection of reaction intermediates. Further application of this new sequential reaction is currently underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06. 102.

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