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Photocatalytic Cascade Radical Cyclization Approach to Bioactive Indoline-Alkaloids over Donor-Acceptor type Conjugated Microporous Polymer

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Supporting Information Placeholder

ABSTRACT: Herein, we describe a visible-light-induced radical strategy for the 1,2-formylarylation of *N*-aryl acryl amides via the C-H activation of 1,3-dioxolane using a carbazolic-cyano conjugated microporous polymer (CC-CMP) as a metal-free photocatalyst. This process provides an efficient and mild approach for constructing highly functionalized formyl-substituted oxindoles, which are valuable building blocks that allow rapid access to various important heterocycle-fused and spirocyclic indole alkaloids. Utilizing this strategy, bioactive alkaloids, such as (\pm)-desoxyeseroline, (\pm)-esermethole and (\pm)-*N*-Me-coerulescine, have been concisely synthesized in up to 74% overall yield from low-cost acrylamides and 1,3-dioxolane. The overall yields of our approach are much higher than those of conventional multi-step methods. Gram-scale syntheses of natural alkaloids have been demonstrated, highlighting the practical utility of this protocol. The use of CC-CMP photocatalysts, which are metal-free, flexible, stable, effective and reusable, makes this strategy appealing to advanced chemical manufacturing.

KEYWORDS: visible-light photocatalysis, 3-formyloxindoles, conjugated microporous polymers, bioactive-alkaloids, metal-free photocatalyst

Heterocycle-fused indolines and spirocyclic oxindoles are ubiquitous in natural products and exhibit a broad range of pharmacological properties, such as anticancer, antimigraine, contraceptive activities.1 (-)-Physostigmine, and а representative fused indoline alkaloid that was isolated by Hesse and co-workers² from seeds of the African Calabar bean, Physostigma venenosum in 1864, is a drug candidate for the treatment of Alzheimer's disease.³ Heterocycle-fused indoline and spirocyclic oxindole derivatives have therefore become attractive targets for drug discovery ⁴ and as building blocks to synthesize other alkaloids and pharmaceuticals.⁵⁻⁷ However, most existing synthetic strategies rely on utilizing indole precursors for the construction of key fused indoline and spirocyclic oxindole skeletons^{6a}. These approaches often suffer from the requirement of both expensive noble-metal catalysts and operationally tedious procedures, which greatly hinder their widespread application. Thus, developing a robust synthetic strategy for the rapid synthesis of these potential bioactive alkaloids under mild conditions, especially utilizing metal-free and reusable catalysts, is highly desirable.

Retrosynthetic analysis indicated that the aforementioned valuable alkaloids share the same building block, 3-formyloxindoles (Figure 1). Although considerable efforts for construct 3-functional-oxindoles have been made,⁸ short synthesis of **3-formyloxindole** structure from low-cost and readily available starting materials under mild conditions are

rare. Formyl group provides a handle for chemical transformations



Figure 1. A) Retrosynthetic analysis for the synthesis of natural fused and spirocyclic oxindole alkaloids. B) Heterogeneous

photocatalyzed synthesis of 3-formyloxindole. TBHP = *tert*-Butyl hydroperoxide.

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because of its rich chemical reactivity.9 Recently, visible-lightinduced construction formyl with good chemical selectivity and high efficiency under mild conditions and low-energy irradiation have received increasing attentions.¹⁰ However, all these elegant works were based on homogeneous photocatalyst, especially the 4CzIPN,11 with donor-acceptor (D-A) molecular dyads. Heterogeneous catalyst materials,¹² particularly the photocatalyst material¹³ have been developed vigorously in recent years due to their reusability and structure controllability. Herein, we designed and developed a carbazolic-cyano conjugated microporous polymer (CC-CMP) as a metal-free, structure controllable and reusable heterogeneous photocatalyst for the 1,2-formylarylation of *N*-aryl acryl amides with formyl equivalent radicals, which were generated from the regioselective C-H activation of 1,3-dioxolane to produce the desired 3-formyloxindoles (Figure 1). Numerous important bioactive fused indoline and spirocyclic oxindole alkaloids, such as (\pm) -desoxyeseroline, (\pm) -esermethole and (\pm) -N-Mecoerulescine, were rapidly accessed with high overall yields from low-cost and readily available precursors. Gram-scale (5 mmol) approaches to oxo-ring fused indoline 3c and (\pm) esermethole (4b), valuable intermediates of (\pm) -physovenine and (\pm) -physostigmine, were achieved in 65% and 54% total yields, respectively.

We began our study with the reaction of *N*-methyl-*N*-phenylmethacrylamide (**1a**) with a photocatalyst and an oxidant in 1,3-dioxolane (neat) at rt for 12 h under 5 W blue LED irradiation (Supporting Information Table S1). Using *tert*-butyl hydroperoxide (TBHP) as the oxidant, a series of photosensitizers were evaluated (Supplementary Table 1). 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene

(4CzIPN)¹⁴ was found to be the best photocatalyst as it afforded target 3-formyloxindole 2a in 77%. The superior performance of 4CzIPN compared to other photosensitizers is probably attributable to its better photostability (Supplementary Figure S6). Unfortunately, the poor recyclability of these organic dyes was limited their widespread application. To this end, converting these homogenous organic dyes into robust and reusable heterogeneous photocatalysts by simple selfpolymerization is of great interest, as it not only retains the high reactivity of the organic dyes but also endows the catalyst with additional advantages, such as enhanced light harvesting and enabling recycling and reuse. Then, as illustrated in Figure 2a. an oxidative coupling polymerization of 4CzIPN was preformed to furnish the conjugated microporous polymer,¹⁵ CC-CMP. Notably, CC-CMP afforded an improved yield (81%) of the oxide-tive cyclization product, and could be easily recycled by filtration and rising with dichloromethane. Characterization including scanning electron microscopy (SEM), UV-visible absorption spectroscopy and thermal gravimetric analysis (TGA) were performed to verify the success of polymerization. As shown in Figures 2b-c, the SEM images illustrated the different morphologies before and after polymerization. The monomer appeared as a solid block structure, while the polymer appeared as porous fibre-like structures with lengths of more than 5 μ m. The UV-visible absorption spectra (Figure 2d) revealed that the polymer showed a significantly expanded absorption range compared to the monomer. The thermal stability was remarkably improved after polymerization, as revealed by TGA (Figure 2e).

Under the optimal conditions, the scope of 1,2formylarylation of *N*-aryl acryl amides via the C-H activation of 1,3-dioxolane was investigated. As shown in Table 1, the reaction worked efficiently with a broad reaction scope. 1) The R^1 group on the acrylamides could be phenyl, chloromethyl or methoxy, and the corresponding 3-formyloxindole **2a–2d** were obtained in 68-81% yields. 2) *N*-Aryl-acrylamide substrates with phenyl, isopropyl or benzyl moieties on the nitrogen behaved similarly to *N*-methyl-*N*-phenylmethacrylamide (**1a**) and provided desired products **2e-2g** in 79, 75, and 72% yield, respectively.



Figure 2. a) Oxidative polymerization of 4CzIPN monomers catalysed by FeCl₃ to produce CC-CMP. b) SEM image of the 4CzIPN monomers. c) SEM image of the 4CzIPN polymer. d) UV-visible absorption spectra of the 4CzIPN monomers and polymer. e) Thermal gravimetry of the 4CzIPN monomers and polymer.

An acrylamide with a tetrahydroquinoline moiety afforded the desired product in 63% yield. 3) The scope of acrylamides with different substituents on the aromatic ring was further examined, and both electron-donating groups, such as methyl and methoxy, and electron-withdrawing groups such as chloro, bromo, trifluoromethyl and other functionalities (i.e. ester and cyano), were well tolerated, giving 3-formyloxindoles 2i-20 in 60-76% yields. The bromo and chloro substituents provided further handle for molecule functionalization. 4) N-Aryl-acrylamide substrates with naphthalene and di-substituted benzene substituents on the nitrogen smoothly gave the corresponding 3-formyloxindoles 2p and 2q. To investigate the regioselectivity of this cascade radical cyclization, two examples with meta-substituted substrates were conducted. The meta-methyl substrates gave a mixture of two regioselective products 2r and 2r' in a ratio of 1.6: 1 with a 70% total yield. Similarly, the meta-trifluoromethyl substrates gave a mixture of two regioselective products 2s and 2s' in a ratio of 1.1: 1 with a 68% total yield. The scalability of this catalytic process was demonstrated by a gram-scale synthesis of 2j in 76% isolated yield (1.77 g). Notably, the heterogeneous photocatalyst

4CzIPN CC-CMP could be recycled and reused by simple filtration and rinsing in dichloromethane, maintaining its high reactivity with at least five cycles (Figure 3).

On the basis of our retrosynthetic analysis. 3formyloxindoles are the key building blocks for constructing oxo-ring and aza-ring fused indoline derivatives. Direct reduction of 3-formyloxindole 2 with excess LiAlH₄ at 0 °C for 5~10 min provided tricyclic oxo-ring fused indoline derivatives 3. On the other hand, condensation of 3-formyloxindole 2 with methylamine hydrochloride, followed by in situ reduction of the crude imine with LiAlH₄ at 65 °C provided tricyclic aza-ring fused indoline derivatives 4 (Table 2). A range of 3formyloxindoles were smoothly converted to the corresponding tricyclic indoline derivatives (3i-3k and 4a-4e) or tetracyclic indole derivatives (3j, 3k and 4f) under the standard conditions. Bis-tricyclic oxo-ring fused indoline derivative 31 can be obtained in 80% yield from bis-(3-formyloxindole). Since trifluoromethyl groups are prevalent in biologically and pharmaceutically relevant molecules as well as in agrochemicals,¹⁶ the oxo-ring fused indoline bearing a trifluoromethyl group was constructed (3d). 3- Formyloxindole 2j was reduced with

Table 1. Scope of the acrylamide substrates







Figure 3. Recyclability of 4-CzIPN CC-CMP

 Table 2. Synthesis of oxo- and aza-ring fused indolines and spirocyclic indole derivatives





4.0 equiv. of LiAlH₄ at 0 °C and provided tricyclic oxo-ring fused indoline **3c**, which could be easily converted into (±)physovenine in two steps.^{6a} Notably, indoline **3c** could be easily prepared by the gram-scale (6 mmol) reduction of **2j** in 86% isolated yield (1.13 g). (±)-Desoxyeseroline (**4a**) and (±)esermethole (**4b**) could be directly synthesized from 3-formyl oxindoles **2a** and **2j** by reductive amination in the presence of methylamine hydrochloride and LiAlH₄ in 78% and 74% yields, respectively. (±)-Physostigmine and (±)-phenserine were synthesized from (±)-esermethole (**4b**) in two steps.^{6a} Our study therefore constitutes a formal synthesis of (±)-physovenine, (±)-

physostigmine and (±)-phenserine in four steps from readilyavailable starting materials.

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Spirooxindole alkaloids such as coerulescine and horsfiline are also attractive targets because of their diverse bioactivities.¹⁷ 3-Chloro-3-formyloxindole (**2c**) was therefore applied as the key intermediate for the construction of spirooxindole alkaloids. The condensation of **2c** with methylamine followed by *in situ* reduction of the imine intermediate with NaBH₃CN and cyclization was performed, which afforded (\pm)-*N*-Mecoerulescine (**5**) in 78% yield (Table 2).

A plausible mechanism of the visible-light-induced 1,2formylarylation of the activated alkene is depicted in Scheme 1. Initially, the photoinduced single-electron transfer (SET) from the excited-state 4CzIPN CC-CMP* to TBHP delivers a tertbutyloxy radical, which is verified by the fact that the reduction potential of CC-4CzIPN* is sufficient to reduce TBHP to furnish tert-butyloxy radical. To further elucidate the SET Stern-Volmer process. fluorescence quenching and fluorescence lifetime experiments using the soluble monomer (4CzIPN) photocatalyst and TBHP were performed. As expected, the fluorescence intensity of 4CzIPN exhibits linear attenuation and the fluorescence lifetime is shortened obviously when the concentration of the TBHP quencher increases (Supporting Information Figure S3).¹⁸ Next, the *tert*-butyloxy radical regioselectivity abstracts a 2-C(sp³)-H of 1,3-dioxolane to generate alkoxyalkyl radical intermediate A.¹⁹ Radicalinduced addition of intermediate A to acrylamide 1a affords radical intermediate **B**, which undergoes intramolecular cyclization to produce radical intermediate C. Oxidation of radical intermediate C by the cationic radical of 4CzIPN CC-CMP⁺⁺ followed by rearomatization gives the dioxolane acetal intermediate. Finally, a hydrolytic workup will furnish the desired 3-formyloxindole product.

Scheme 1. Plausible mechanism of the visible-light-induced 1,2-formylarylation of *N*-aryl acryl amides



In summary, we have demonstrated a rapid and concise construction of 3-formyloxindoles via the photo-induced dual-C-H functionalization of *N*-aryl acryl amides and 1,3-dioxolane using a heterogeneous photocatalyst in a metal-free manner. The obtained 3-formyloxindoles serve as key building blocks for the rapid syntheses of a variety of bioactive alkaloids, including (\pm)-desoxyeseroline, (\pm)-esermethole and (\pm)-*N*-Me-coerulescine, with overall yields (up to 74%) dramatically higher than those achieved with conventional multi-step methods. The reusability of the CC-CMP photocatalyst and gram-scale synthesis of natural alkaloids are illustrated, highlighting the practical potential of this strategy. This work demonstrates the great potential of using polymer semiconductors, CMPs, as visible-light harvesting photocatalysts that are highly stable, reusable and metal-free and offer tuneable charge separation for the sustainable synthesis of bioactive heterocycles and pharmaceutical compounds.

ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Table of Contents Me =0 CHO Ņе $R^3 = OMe$ 1.7 g scal ♠ Easily available starting materials ♥ Useful formyl product R= H, (±)-desoxyeseroline Mild conditions and scalable 2 steps from N-arylacrylamide Reusable metal-free photocatalyst 64% overall yield R= OMe, (±)-esermethole 2 steps from *N*-arylacrylamide 58% overall yield