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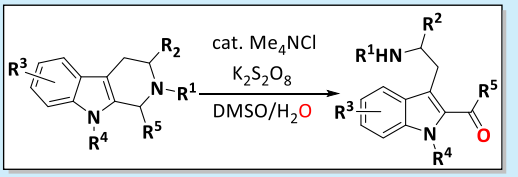
Oxidation of Tetrahydro-β-carbolines by Persulfate

Haijun Chen,* Fu Ye, Jing Luo, and Yu Gao

Key Laboratory of Molecule Synthesis and Function Discovery (Fujian Province University), College of Chemistry, Fuzhou University, Fuzhou, Fujian 350116, China

Supporting Information

ABSTRACT: The development of persulfate-mediated oxidation of tetrahydro-β-carbolines is reported. This mild reaction facilitates the formation of a variety of 2-formyl *N*-substituted tryptamines and the related derivatives as key intermediates in moderate to excellent yields. The method is applicable to direct last-stage oxidation of two interesting pharmaceuticals, Cialis and evodiamine.



Oxidation as one class of important reactions enables a range of powerful transformations.[1] Traditional oxidation reactions often use expensive or toxic oxidants such as chromium/manganese/lead salts. Recently, more and more researchers are trying to utilize inexpensive and nontoxic reagents for oxidation.[2]

Selenium dioxide is a useful and versatile oxidizing reagent in organic synthesis.[3] It participates in various types of oxidation reactions, including allylic hydroxylation, benzylic oxidation, oxidative rearrangement, oxidative demethylation, and oxidative cleavage.[4] Because of the toxicity of this reagent, many reactions have been gradually replaced by other better reagents in recent years.[5] However, the selenium dioxide oxidation with active methyl or methylene still plays an important role in the transformation of organic chemical functional groups.[6] For example, in order to obtain 2-formyl *N*-substituted tryptamines as key intermediates for further transformation,[7] SeO_2-mediated oxidation of tetrahydro-β-carboline derivatives (THβCs) is the most commonly used method (Figure 1).[8] Therefore, from environmentally friendly and economic viewpoints, the utilization of other alternative oxidants instead of SeO_2 would be more appealing. In continuation of our research on the functionalization of THβCs,[9] herein we report an efficient persulfate-mediated oxidation of THβCs for the synthesis of 2-formyl *N*-substituted tryptamines and the related derivatives under mild conditions.

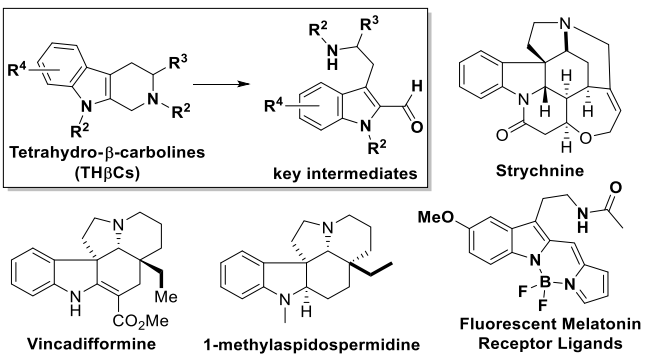


Figure 1. 2-Formyl *N*-substituted tryptamines and the related derivatives as key intermediates for the synthesis of representative natural products and pharmaceuticals.

Persulfate has been demonstrated to be a useful and versatile oxidant in organic chemistry because of its characteristics of easy availability, good stability, and low toxicity.[10] We envisioned that careful consideration of the following points might be beneficial for oxidation of THβCs: (a) a judicious choice of the solvent and (b) the choice of an additive that could enable the transformation under metal-free and mild conditions.[11]

We commenced our evaluation of the reaction parameters employing THβC **1** as the model substrate (Table 1). An extensive screening of solvents, oxidants, and additives revealed that the use of $K_2S_2O_8$ as the oxidant, additive Me_4NCl as the phase-transfer catalyst, and DMSO/H_2O as the mixed solvent provided Boc-2-formyl-Trp-OH **2** in 90% yield (entry 1). DMSO/H_2O as the mixed solvent was found to have an important influence on this transformation (entries 2−5). The use of less water slightly decreased the yield of the oxidation (entries 6 and 7). No reaction occurred without oxidant (entry 8). Among various oxidants tested, $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ were found to be less effective than $K_2S_2O_8$ (entries 9 and 10). A slight decrease in the yield was obtained without Me_4NCl, while larger amounts of Me_4NCl or other additives did not improve the yield (entries 11−13). Notably, using an equivalent amount of $K_2S_2O_8$ also gave a comparable yield (entry 14).

With the optimal conditions in hand, we explored the scope of this new oxidative ring-opening reaction. As shown in Figure 2, a series of THβCs were smoothly transformed into the corresponding aldehydes in moderate to excellent yields. For example, *N*-substituted 2-formyl-Trp-OH(Me) **2**−**4** were obtained in good yields. Different *N*-substituted derivatives were tolerated, and the desired products **5**−**11** were isolated in 65%−92% yield. A THβC bearing an *N*-methyl substituent on the indole ring also reacted smoothly to provide **12** in 54%

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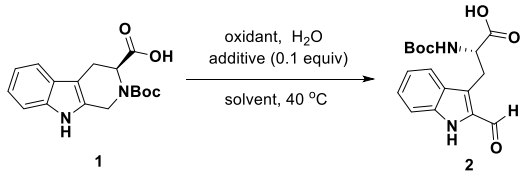
Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	oxidant	additive	equiv of H_2O	yield (%)[b]
1	DMSO	$K_2S_2O_8$	0.1	20	93 (90[c])
2	DMF	$K_2S_2O_8$	0.1	20	trace
3	DMA	$K_2S_2O_8$	0.1	20	46
4	H_2O	$K_2S_2O_8$	0.1	0	trace
5	DMSO	$K_2S_2O_8$	0.1	0	0
6	DMSO	$K_2S_2O_8$	0.1	5	75
7	DMSO	$K_2S_2O_8$	0.1	10	84
8	DMSO	–	0.1	20	0
9	DMSO	$Na_2S_2O_8$	0.1	20	82
10	DMSO	$(NH_4)_2S_2O_8$	0.1	20	38
11	DMSO	$K_2S_2O_8$	0	20	66
12	DMSO	$K_2S_2O_8$	0.2	20	89
13	DMSO	$K_2S_2O_8$	0.1[d]	20	<80
14	DMSO	$K_2S_2O_8$[e]	0.1	20	82

[a]Reactions were carried out by adding the oxidant (2.0 equiv) to a stirred solution of **1** (0.1 mmol), H_2O (0–20 equiv), and the additive (Me_4NCl, 0.1 equiv) in 1.0 mL of the solvent at 40 °C. [b]Determined by ^1H NMR analysis of the crude products using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]Other additives instead of Me_4NCl; see the Supporting Information for details. [e]$K_2S_2O_8$ (1.0 equiv).

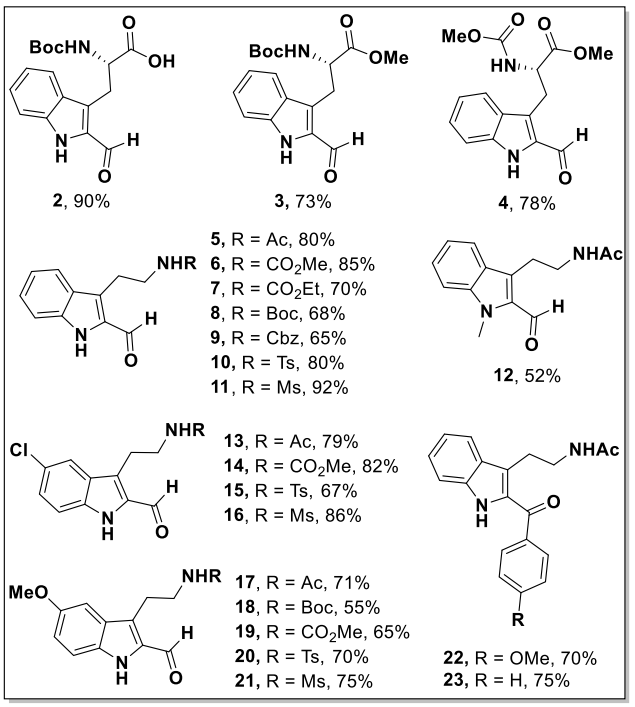


Figure 2. Reaction scope of persulfate-mediated oxidation.

yield. THβCs with a substituent on ring A were compatible with this reaction, and the corresponding aldehydes **13**–**21** were obtained in good to high yields. The efficiency and usefulness of this transformation was further demonstrated by the synthesis of *N*-substituted 2-ketone derivatives. Compounds **22** and **23** were obtained in 70% and 75% yield, respectively. Notably, in comparison with the traditional multistep reaction or the direct formylation reaction,[7e,f] this oxidation is more general and has milder operational conditions.

To prove both the practicality and effectiveness of this approach for large-scale synthesis, we prepared *N*-Boc-2-formyl-Trp-OH **2** on a gram scale under the optimized reaction conditions without a significant decrease in efficiency (87% vs 90%, Figure 3; also see the detailed graphical procedure in the Supporting Information).

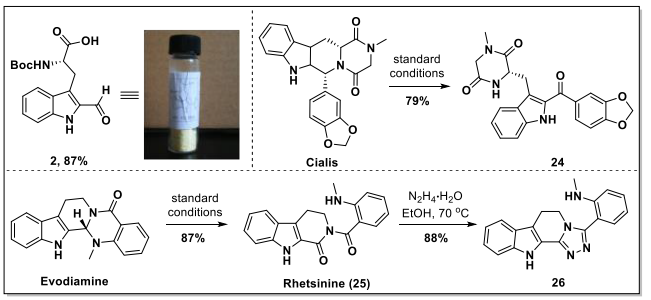


Figure 3. Gram-scale reaction and last-stage oxidation.

To further exemplify the synthetic utility of this oxidation, two important pharmaceutical drugs were selected for last-stage oxidation (Figure 3). Compound **24** was readily prepared from the marketed small-molecule drug Cialis in a satisfactory yield by our convenient oxidation. Rhetsinine (**25**)[12] was obtained in high yield through last-stage oxidation of evodiamine without purification by column chromatography. Further transformation of rhetsinine afforded one interesting lead compound **26** with antibacterial activity.[13]

Several control experiments were carried out to investigate the mechanism of this reaction. First, the oxidation of THβCs is completely inhibited in the presence of TEMPO or ascorbic acid, indicating that a free radical is involved in this reaction. Second, this reaction afforded [^{18}O]**2** when $H_2{}^{18}O$ was used, indicating that the oxygen atom comes from H_2O (Figure 4A). On the basis of the above results and literature reports, a

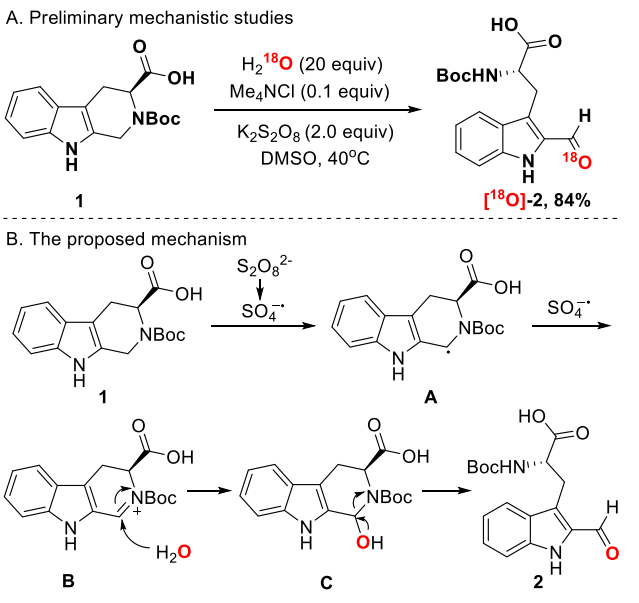


Figure 4. Mechanistic investigations and the proposed mechanism.

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proposed mechanism for this mild oxidation is shown in Figure 4B.[14] Decomposition of $S_2O_8^{2-}$ leads to the formation of sulfate radical anion $SO_4^{-\bullet}$ under thermolysis in the DMSO solvent.[11] The carbon-centered radical **A** is generated from THβC **1** by single electron transfer (SET) to $SO_4^{-\bullet}$, followed by further oxidation to afford **B**.[15] Intermolecular nucleophilic addition to **B** finally delivers *N*-Boc-2-formyl-Trp-OH **2**.

In summary, a novel persulfate-mediated oxidation of THβCs has been developed for the synthesis of a broad range of 2-formyl *N*-substituted tryptamines and the related derivatives under mild conditions. It was found that both the oxidant and the cosolvents (DMSO/H_2O) were critical factors for this oxidation. The synthetic utility of this approach was further demonstrated by last-stage oxidation of the marketed small-molecule drug Cialis and the natural product evodiamine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02772.

Optimization studies, mechanistic studies, synthesis procedures, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chenhaij@gmail.com.

ORCID

Haijun Chen: 0000-0001-7945-2461

Yu Gao: 0000-0002-1137-7669

Notes

The authors declare no competing financial interest.

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