Journal Pre-proofs

Visible-Light-Induced Aerobic Epoxidation in Cyclic Ether: Synthesis of Spiroepoxyoxindole derivatives

Kaixiu Luo, Xianglin Yu, Peng Chen, Kun He, Jun Lin, Yi Jin

PII: DOI: Reference:	S0040-4039(19)31377-2 https://doi.org/10.1016/j.tetlet.2019.151578 TETL 151578
To appear in:	Tetrahedron Letters
Received Date: Revised Date: Accepted Date:	27 November 201921 December 201927 December 2019



Please cite this article as: Luo, K., Yu, X., Chen, P., He, K., Lin, J., Jin, Y., Visible-Light-Induced Aerobic Epoxidation in Cyclic Ether: Synthesis of Spiro-epoxyoxindole derivatives, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151578

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Elsevier Ltd. All rights reserved.

Graphical Abstract

To create your abstract, type over the instructions in the template box below. Fonts or abstract dimensions should not be changed or altered.





Tetrahedron Letters journal homepage: www.elsevier.com



Visible-Light-Induced Aerobic Epoxidation in Cyclic Ether: Synthesis of Spiroepoxyoxindole derivatives

Kaixiu Luo, Xianglin Yu, Peng Chen, Kun He, Jun Lin* and Yi Jin*

Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry Education and Yunnan Province, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China.

ARTICLE INFO

Article history: Received Received in revised form Accepted Available online

Keywords: Visible-light-induced; Epoxidation; Spiroepoxyoxindole derivatives; Initiation

ABSTRACT

A visible-light-induced aerobic epoxidation of 3-benzylideneindolin-2-ones with a meso-Tetraphenylporphyrin (TPP) photosensitizer in cyclic ether has been established for the efficient synthesis of spiro-epoxyoxindole derivatives. This reaction leads to excellent intermolecular *trans*- stereoselective epoxide ring formation. This strategy also proceeds effectively with a good functional group tolerance under mild reaction conditions. Mechanistic investigations indicate that light is required for reaction initiation.

2009 Elsevier Ltd. All rights reserved.

1. Introduction

Heterocyclic spirooxindoles bearing a spirocyclic system are well-recognized scaffolds that are widely found in natural alkaloids, synthetic bioactive molecules and clinical pharmaceuticals¹⁻⁶. In particular, spiro-epoxyoxindoles (Fig. 1) that feature a spiro-carbon and oxirane ring have been identified not only as privileged frameworks with significant biological activities (e.g., antifungal, antitubercular, anti-Fusarium oxysporum and anticancer activities)⁷⁻⁹, but also as important precursors for the synthesis of complex drug molecules and natural products¹⁰⁻¹². For example, Wang's group carried out a total synthesis of (+)-gliocladin C by using spiro-epoxyoxindoles as the starting substrates¹³.





Spiro-epoxyoxindoles have attracted tremendous research interest in the synthetic community due to their potency (synthetic potential) and wide range of bioactivities. Thus, various powerful strategies have been developed to access these skeletons¹⁴⁻¹⁶ (Schemes a and b). However, these methods depend on the use of a transition metal or a stoichiometric amount of chemical oxidants such as organic and inorganic peroxides, giving rise to safety, environmental and economic concerns. Recently, visible-light-induced photocatalysis has emerging as an attractive, green and powerful method for the realization of challenging chemical transformations¹⁷⁻²². In particular, the generation of singlet oxygen (¹O₂) under mild photocatalytic conditions for oxygenation reactions has been developed as an alternative synthetic strategy²³⁻²⁸. For example, Luo's group reported that the epoxidation of α , β -unsaturated ketones was mediated by amidines via visible light²⁹. Therefore, development of efficient epoxidations by using O₂ instead of an additive for the synthesis of spiro-epoxyoxindoles is highly desirable.

Scheme 1. Preparation methods of spiro-epoxyoxindole derivatives



In this context, continuing our previous research on epoxidation³⁰, here we describe a visible-light-induced aerobic epoxidation for the effective production of spiro-epoxyoxindole derivatives in cyclic ether without either an additive or metal catalysts. This new general approach allows the formation of epoxy via air atmosphere and gives products in excellent yield in a single step. Our novel protocol offers an efficient pathway for constructing spiro-epoxyoxindole derivatives under mild conditions.

2. Results and Discussion

ĺ	N 1a	Ps, Air, Base Solvent, 18 W blue LED Temperature, 2	s, 2a tra	Ph H O +	2'a cis	1 ∑Ph =Ο	
Entry	Ps	Solvent	Base	T/°C	2a:2'a[c]	Yield (%) ^{[b], [c]}	
1	TPP	EtOH	K_3PO_4	rt	nd	nr	
2	TPP	DCM	K_3PO_4	rt	nd	nr	
3	TPP	Acetone	K_3PO_4	rt	nd	nr	
4	TPP	Toluene	K_3PO_4	rt	nd	nr	
5	TPP	Ethyl ether	K_3PO_4	rt	nd	nr	
6	TPP	THP	K_3PO_4	rt	>20:1	74	
7	TPP	THF	K_3PO_4	rt	>20:1	82	
8	TPP	1,4-dioxane	K_3PO_4	rt	>20:1	66	
9	TPP	TBME	K_3PO_4	rt	nd	nr	
10	TPP	THF	Et ₃ N	rt	>20:1	72	
11	TPP	THF	tBuOK	rt	>20:1	93	
12	TPP	THF	NaOH	rt	>20:1	86	
13	TPP	THF	K_2CO_3	rt	>20:1	73	
14	TPP	THF	DBU	rt	>20:1	56	
15	TPP	THF	NaH ₂ PO ₄	rt	>20:1	45	
16	TPP	THF	none	rt	nd	nr	
17	TPP	THF	tBuOK	40	>20:1	88	
18	TPP	THF	tBuOK	60	>20:1	79	
19	TPP	THF	tBuOK	90	>20:1	59	
20	Pc	THF	tBuOK	rt	24	80	
21	H_2TPP	THF	tBuOK	rt	24	85	
22	Eosin B	THF	Et ₃ N	rt	24	68	
23	Eosin Y	THF	tBuOK	rt	24	61	
24	TPP/N ₂	THF	tBuOK	rt	24	nr	
25	TPP/O.	THE	tBuOK	rt	24	97	

Table 1. Optimized conditions for the synthesis of 2a^[a]

[a] Reaction conditions: 1a (0.5 mmol), TPP (1 × 10⁻² mmol), base (0.6 mmol), and solvent (2 mL) were stirred for 24 h at room temperature under air atmosphere. [b] Isolated yield based on 1a. [c] nr = no reaction, nd = no detected.

In our initial studies, the model reaction of 3-benzylideneindolin-2-one **1a** was investigated by using TPP as the photosensitizer and 18 W blue LEDs as the light source at room temperature under air atmosphere in order to screen different solvents (Table 1, entries 1–9). To our delight, the desired product **2a** was obtained in good yield in cyclic ethers, and especially in THF (82%), while we could not obtain spiro-epoxyoxindole **1a** using aliphatic ethers and other solvents. Encouraged by this result, we sought to enhance the yield of this reaction and carried out a screening of the bases such as Et_3N , tBuOK, NaOH, K_2CO_3 , DBU and NaH_2PO_4 (Table 1, entries 10–15). We found that all of these reactions proceeded smoothly while *t*-BuOK delivered the best results (93%). By contrast, the reactions cannot be carried out in the absence of the bases (Table 1, entries 16). Different photosensitizers were investigated, and it was found that TPP provided the highest yield (Table 1, entries 11, 20–23). Additionally, room temperature was determined to be the best temperature for the reaction (Table 1, entries 11, 17-19). The target compound **2a** was formed in excellent yield under an O_2 atmosphere (Table 1, entries 25). By contrast, spiro-epoxyoxindole **2a** was not detected under an N_2 atmosphere (Table 1, entries 24), demonstrating that oxygen plays a key role of a green oxidant in this reaction. Notably, this reaction leads to excellent intermolecular *trans*- stereoselective epoxide ring formation. The trans- configuration of compound **2a** was confirmed by NOE spectra (Figure S2, SI file).

Table 2. Preparation of spiro-epoxyoxindoles 2





[a] Reaction conditions: 1 (0.5 mmol), TPP (1×10^{-2} mmol), base (0.6 mmol), and solvent (2 mL) were stirred for 24 h at room temperature under air atmosphere. [b] Isolated yield based on 1a. [c] nr = no reaction.

With the optimal reaction conditions established, the feasibility of this epoxidation was explored by changing various R_1 and R_2 substituents in 3-benzylideneindolin-2-ones (Table 2). First, we found that the 3-benzylideneindolin-2-ones bearing chlorine or hydroxyl groups on R_1 were well-tolerated in a good yield (**2b** 95%, **2c** 83%). Next, we examined the performance of the R_2 substituents at the para, meta, and ortho positions on the aromatic ring. Gratifyingly, all of the reactions proceeded smoothly to generate the target compounds **2d-w** in moderate-to-excellent yields. It was found that the electron-donating groups (Me, Et or OMe) gave higher product yields (**2h-j**, **2m**) than the electron-withdrawing groups (F, Cl or NO₂ **2e-g**). The position of the substituents had a significant influence on the yield with the substituents on the meta or para positions more suitable than those at the ortho position (**2b-m**). Nevertheless, all of the reactions had high yields. By contrast, low yields were observed with multiple substituted substrates **1** due to the steric hindrance effects (**2k-l, 2q-s**). Reactions of heterocyclic substrates produced the desired products **2u** and **2v** with moderated yields. Finally, alkyl substituted substrates can also give desired products (**2x, 2y**) under standard condition in good yield. Interestingly, both aryl and alkyl substrate gave the corresponding epoxides in excellent *trans*- steroselectivity (dr, *trans:cis* > 20:1).



Figure 2. ORTEP diagram of 2a

The chemical structures of the spiro-epoxyoxindole derivatives were examined by ¹H NMR, ¹³C NMR, and HRMS analyses. The structure of **2a** was unambiguously confirmed by single-crystal X-ray analysis, as shown in Fig. 2 (CCDC 966890).

Scheme 2. Control Experiments



Several control experiments were carefully conducted in order to obtain an in-depth understanding of the reaction mechanism (Scheme 2). When the reaction of 3-benzylideneindolin-2-ones **1a** was investigated with the standard conditions under N_2 atmosphere, the desired product **2a** was not detected, suggesting that O_2 from air is needed in this reaction. By contrast, under O_2 atmosphere, the reaction provided **2a** with the highest yield of 97% and the peroxide intermediate THF-OOH was detected by NMR. The reaction cannot be carried out in the dark and also did not proceed effectively in the absence of TPP. Meanwhile, a control experiment by using isolated THF-OOH in the absence of TPP was performed, and the reaction can proceed smoothly. These results indicate that molecular oxygen and light are necessary for this epoxidation.

Scheme 3. Proposed mechanism for the construction of spiro-epoxyoxindole derivatives 2



Based on the above experimental results, a plausible mechanism was proposed as shown in Scheme 3. Initially, molecular oxygen is activated from the triplet state (${}^{3}O_{2}$) to the singlet state (${}^{1}O_{2}$) by TPP through energy transfer under visible light. Next, the α -THF C–H bond was peroxided by singlet O_{2} to produce the hydroperoxide THF-OOH³¹. After the deprotonation, peroxide oxygen anion was added to substrate 1 to provide intermediate I, and then the oxygen anion was eliminated to produce a spiro-epoxyoxindole 2. Among this transformation, the nucleophilic addition of THF-OO-anion makes the two possible *trans/cis* transition states of the intermediate I (Scheme 3). In the *trans* transition state, due to the presence of hydrogen bonding cyclization of the (furan oxygen atom)–(H+ ion)–(indole oxygen negative atom), this configuration is more favorable, which results in the product mainly as the *trans* selectivity. Lastly, Tetrahydrofuran-2-ol was obtained via abstracting a proton.

Scheme 4. Gram-Scale Reaction



To demonstrate the potential synthetic application of this strategy, a gram-scale reaction of 1a was carried out (Scheme 4). The visible-light-induced aerobic epoxidation of 1a on a 10.0 mmol scale gave 2.16 g of the desired product 2a in 91% yield under the standard reaction conditions.

3. Conclusions

In conclusion, a visible-light-induced aerobic epoxidation was developed for the preparation of spiro-epoxyoxindole derivatives. This highly effective process proceeds well to afford spiro-epoxyoxindole derivatives without any additive under mild conditions and shows good functional group tolerance. Our mechanistic study suggests that light irradiation is critical for the reaction initiation. The reaction can be performed on the gram scale and proceeds smoothly under these reaction conditions, suggesting the high likelihood of the rapid transition of this novel protocol to use in heterocyclic chemistry applications.

4. Acknowledgements

This work was supported by the Program for Changjiang Scholars and Innovative Research Team in University (IRT17R94); the National Natural Science Foundation of China (Nos. 21662044, 81560601, 21262043, 81760621, and U1202221); Training Program for Young and Middle-aged Academic and Technical Leaders in Yunnan Province (2015HB004); the Foundation of "Yunling Scholar" Program of Yunnan Province (C6183005); Program for Excellent Young Talents, Yunnan University; and thank the High Performance Computing Center at Yunnan University for use of the high performance computing platform.

5. References and notes

- 1. Yang Y.-T.; Zhu J.-F.; Liao G.; Xu H.-J. and Yu B. Curr. Med. Chem. 2018, 25, 2233-2244.
- 2. Wang L.; Li S.; Bluemel M.; Puttreddy R.; Peuronen A.; Rissanen K. and Enders D. Angew. Chem. Int. Edit. 2017, 56, 8516-8521.
- 3. Samineni R.; Madapa J.; Pabbaraja S. and Mehta G. Org. Lett. 2017, 19, 6152-6155.
- 4. Yu B.; Yu D.-Q. and Liu H.-M. Eur. J. Med. Chem. 2015, 97, 673-698.
- 5. Zhao Y.; Liu L.; Sun W.; Lu J.; McEachern D.; Li X.; Yu S.; Bernard D.; Ochsenbein P.; Ferey V.; Carry J.-C.; Deschamps J. R.; Sun D. and Wang S. J. Am. Chem. Soc. 2013, 135, 7223-7234.
- 6. Dalpozzo R.; Bartoli G. and Bencivenni G. Chem. Soc. Rev. 2012, 41, 7247-7290.
- 7. Zhu Y.; Wang Q.; Cornwall R. G. and Shi Y. Chem. Rev. 2014, 114, 8199-8256.
- 8. Srour H.; Le Maux P.; Chevance S. and Simonneaux G. Coordin. Chem. Rev. 2013, 257, 3030-3050.
- 9. Hong L. and Wang R. Adv. Synth. Catal. 2013, 355, 1023-1052.
- 10. Singh G. S. and Desta Z. Y. Chem. Rev. 2012, 112, 6104-6155.
- 11. Luo M.; Yuan R.; Liu X.; Yu L. and Wei W. Chem.-Eur. J. 2016, 22, 9797-9803.
- 12. Hajra S.; Maity S. and Maity R. Org. Lett. 2015, 17, 3430-3433.
- 13. Zhu G.; Bao G.; Li Y.; Sun W.; Li J.; Hong L. and Wang R. Angew. Chem. Int. Edit. 2017, 56, 5332-5335.
- 14. Gasperi T.; Loreto M. A.; Migliorini A. and Ventura C. Eur. J Org. Chem. 2011, 385-391.
- Palumbo C.; Mazzeo G.; Mazziotta A.; Gambacorta A.; Loreto M. A.; Migliorini A.; Superchi S.; Tofani D. and Gasperi T. Org. Lett. 2011, 13, 6248-6251.
- 16. Muthusamy S.; Karikalan T. and Suresh E. Tetrahedron Lett. 2011, 52, 1934-1937.
- 17. Cambie D.; Bottecchia C.; Straathof N. J. W.; Hessel V. and Noel T. Chem. Rev. 2016, 116, 10276-10341.
- 18. Romero N. A. and Nicewicz D. A. Chem. Rev. 2016, 116, 10075-10166.
- 19. Marzo L.; Pagire S. K.; Reiser O. and Konig B. Angew. Chem. Int. Ed. Engl. 2018, 57, 10034-10072.
- 20. Chatterjee T.; Iqbal N.; You Y. and Cho E. J. Acc. Chem. Res. 2016, 49, 2284-2294.
- 21. Zhou Q. Q.; Zou Y. Q.; Lu L. Q. and xiao W. J. Angew. Chem. Int. Ed. Engl. 2019, 58, 1586-1604.
- 22. Strieth-Kalthoff F.; James M. J.; Teders M.; Pitzer L. and Glorius F. Chem. Soc. Rev. 2018, 47: 7190-7202.
- 23. Ogilby P. R. Chem. Soc. Rev. 2010, 39, 3181-3209.
- 24. Ghogare A. A. and Greer A. Chem. Rev. 2016, 116, 9994-10034.
- 25. Bian C.; Singh A. K.; Niu L.; Yi H. and Lei A. Asian J. Org. Chem. 2017, 6, 386-396.
- 26. Pibiri I.; Buscemi S.; Piccionello A. P. and Pace A. Chemphotochem, 2018, 2, 535-547.
- 27. Yan D. M.; Zhao Q. Q.; Rao L.; Chen J. R. and Xiao W. J. Chem.-Eur. J. 2018, 24, 16895-16901.
- 28. Zhang X.; Rakesh K. P.; Ravindar L. and Qin H. L. Green Chem. 2018, 20, 4790-4833.
- 29. Wu Y.; Zhou G.; Meng Q.; Tang X.; Liu G.; Yin H.; Zhao J.; Yang F.; Yu Z. and Luo Y. J. Org. Chem. 2018, 83, 13051-13062
- 30. Luo K.; Zhao Y.; Zhang J.; He J.; Huang R.; Yan S.; Lin J. and Jin Y. Org. Lett. 2019, 21, 423-427.
- 31. Sagadevan A.; Hwang K. C. and Su M.-D. Nat. Commun. 2017, 8, 1-8.

Declaration of interests

 \boxtimes The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

□ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- ► A novel epoxidation was developed to synthesize spiro-epoxyoxindole derivatives.
- ► Good functional group tolerance was found in our protocol.
- ► Light irradiation is critical for the reaction initiation.