Tetrahedron Letters 67 (2021) 152878

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

4CzIPN catalyzed photochemical oxidation of benzylic alcohols

Heng Zhang^a, Tianyun Guo^a, Mingzhong Wu^b, Xing Huo^b, Shouchu Tang^{a,*}. Xiaolei Wang^{b,*}, Jian Liu^{a,*}

^a School of Pharmacy, Lanzhou University, Lanzhou 730000, PR China

^b State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

ARTICLE INFO

Article history: Received 14 December 2020 Revised 21 January 2021 Accepted 24 January 2021 Available online 4 February 2021

Keywords: Photocatalysts Oxidation Air Benzylic alcohols

Introduction

Hydroxyl is a ubiquitous functional group in chemistry, and the synthesis of carbonyl compounds via alcohol oxidation is one of the most important transformations in both academia and industry. However, a stoichiometric amount of environmentally unfriendly oxidants, such as MnO₂, TPAP, hypervalent iodine reagents (Scheme 1A) [1], simultaneously, with the release of harmful wastes such as dimethyl sulfide, are often used in the traditional oxidation of alcohols. This gives rise to the development of environment-friendly catalytic methods that are performed by using transition-metal-free, green, and sustainable processes.

Due to the advantages of green and sustainable characteristics, photocatalysis-based chemical transformations had attracted much attention and made tremendous progress over the past two decades. Meanwhile, the oxygen (O_2) as an ideal oxidant due to its environment-friendliness, can be irradiated to reactive oxygen species (ROS) by photocatalysis, and this process has been widely used in chemical oxidation [2]. Based on these findings, many metal-based photocatalysts (Pt [3], Ti [4], Cu [5], Ru [6], Bi [7], Au [8]) have been developed to oxidize alcohols into ketones/ aldehydes (Scheme 1B). Although widely accepted, it suffers from some limitations due to the economics and toxicity of these metal catalysts. A more elegant and metal-free strategy is highly demanded in photocatalyzed oxidation. Therefore, many efforts

ABSTRACT

A green photoredox oxidation of benzylic primary and secondary alcohols to aldehydes and ketones with air as an oxidant was reported. The oxidation shows broad substrate scope and excellent selectivity over benzylic alcohols to the aliphatic alcohols. Further mechanistic studies revealed a quinuclidine mediated HAT process, and blue LEDs promoted 4CzIPN (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene) photoredox cycle were involved in our oxidation.

© 2021 Elsevier Ltd. All rights reserved.

have been made to search for an organic photocatalyst, and several photocatalysts like EY [9], Flavin [10], Rose Bengal [11], 9-fluorenone [12], thioxanthenone [13] have emerged in photo enabled oxidation (Scheme 1C).

Recently, the photoredox-mediated hydrogen atom transfer (HAT) process shows powerful strength in C-H bond functionalization [14]. MacMillan [15] and Wendlandt [16] used quinuclidine as a HAT mediator, successfully achieved the selective hydrogen abstraction to the α -hydroxyl group and further C-modification. Inspired by these researches, we envisaged that the easily formed α -hydroxyl carbon radical specie may be trapped by a type of reactive oxygen species (ROS) to realize the oxidation of the alcohol. Therefore, here we report a green method to oxidize alcohols into corresponding carbonyl products via a quinuclidine mediated photocatalyzed HAT process (Scheme 1D).

Results and discussion

To begin with, the reaction of benzyl alcohol 1a with 4CzlPN and guinuclidine was tested. Irradiation of the sample solution in MeCN/DMSO with blue LEDs under room temperature and air atmosphere, the desired benzaldehyde 2a was obtained in 44% yield (Table 1, Entry 1). Adding a hydrogen bond acceptor tetrabutylammonium *p*-chlorobenzoate (4-ClOBzBu₄N) slightly decreased the yield (Table 1, Entry 2). Alternation of the reaction solvents to MeCN (Table 1, Entry 3), DMF (Table 1, Entry 4) did not improve the yield a lot. Otherwise, a slightly better result could be obtained in DMSO with a yield of 50% (Table 1, Entry 5). Meanwhile, in order to facilitate work-up and separation, a mixed







^{*} Corresponding authors. E-mail addresses: Tangshch@lzu.edu.cn (S. Tang), wangxiaolei@lzu.edu.cn (X. Wang), jianliu@lzu.edu.cn (J. Liu).

A. Classic Swern, Jones, PCC, DMP, etc. oxidation



Scheme 1. Oxidation of alcohols to carbonyl compounds.

solvent of MeCN/DMSO was chose in our reaction. Replacing 4-ClOBzBu₄N with tetrabutylammonium phosphate (Bu₄NH₂PO₄), no significant improvement was observed (Table 1, Entry 6). Fortunately, when 4 Å molecular sieves were added to the system, the yield increased sharply from 50% to 88% (Table 1, Entry 7), we considered it improved the reaction efficiency by removing water and boosting the decomposition of hydrogen peroxide described by Cibulka [10b]. Meanwhile, O₂ (balloon) atmosphere also revealed favorable yield (Table 1, Entry 8), but the air atmosphere was eligible for reaction convenience in subsequent experiments.

With these optimized conditions in hand, we then explored the substrate scope (Table 2). Various methoxy substituted benzyl alcohols (1b-e) were firstly tested under the optimized reaction conditions and could be oxidized with high yields up to 90%. Interestingly, ortho-substitution in the aromatic ring did not hamper the reaction process, which displayed distinct results compared with previous work [13]. The benzyl alcohol substituted with an amino group (1f, 1g) was then tested which has never been tried under photocatalyzed oxidation. A time prolong was needed for 4-(Boc-amino) benzyl alcohol 1f to get the product with 82% yield, while 2-(Boc-amino) benzyl alcohol 1g bearing steric hindrance reacted moderately under standard conditions with the yield of 75%. When phenyl substituted benzyl alcohol was tested, 4biphenylmethanol 1h also showed excellent reactivity. On the contrary, benzhydryl 1i had a slightly decreased reactivity, the desired benzophenone 2i was obtained with a yield of 66%. Even if reaction

Table 1

7

8

Optimization of the reaction conditions.^a

OH 4CzIPN O quinuclidine additives, solvent rt,10 h blue LEDs 2a						
Entry	Solvent ^b	Additives ^c	Atmosphere	Yield ^d (%)		
1	MeCN/DMSO	w/o	Air	44		
2	MeCN/DMSO	4-ClOBzBu ₄ N	Air	31		
3	MeCN	4-ClOBzBu ₄ N	Air	30		
4	DMF	4-ClOBzBu ₄ N	Air	39		
5	DMSO	4-ClOBzBu ₄ N	Air	50		
6	MeCN/DMSO	Bu ₄ NH ₂ PO ₄	Air	51		

Reaction condition: benzyl alcohol (0.2 mmol), 4CzIPN (3 mol%), quinuclidine (10 mol%), solvent (1 mL), Air (balloon) or O2 (balloon), room temperature (rt), under 8 W blue LEDs irradiation. For the detailed optimization, see Table S1 and Table S2.

2

Bu₄NH₂PO₄ + MS

Bu₄NH₂PO₄ + MS

^b MeCN/DMSO: MeCN (1 mL) + DMSO (0.1 mL).

Bu₄NH₂PO₄ (25 mol%), 4-ClOBzBu₄N (25 mol%), 200 mg 4 Å Molecular sieves were activated under vacuum at 200 °C for 30 min prior to use.

^d Yield determined by GC using *n*-dodecane as an internal standard.

MeCN/DMSO

MeCN/DMSO

time was extended, or performed under an oxygen atmosphere, the yield was still not significantly improved, we speculated that there should be a steric hindrance during the HAT process. To broaden the substrates spectrum, we then investigate the oxidation of 1naphthalenemethanol 1j and cyclic benzyl alcohol. To our delight, the rigid benzyl alcohol analogues with the steric hindrance of benzylic position did not hamper the reaction (1k-n), and the desired ketone products were isolated in good yields. Compared with benzhydryl, a rigid structure was conducive to the reaction. Subsequently, benzyl alcohols with electron-withdrawing groups were tested. 4-Bromobenzyl alcohol 10 and 2-chlorobenzyl alcohol 1p were converted into products with 70% and 86% yields respectively, and the latter showed good reactivity [13]. Other substrates with an electron withdrawing substitute (1q-t) were found to be over-oxidized under standard conditions. If we removed Bu₄NH₂-PO₄, meanwhile extended the reaction time, desired aldehvdes could be obtained with moderate vields. Though this result was unexpected, a clear mechanism was still under investigation. Furthermore, heteroaromatic alcohol analogue **1u** and α -hydroxy ester analogue 1v could also be converted to the desired aldehyde smoothly. What is striking about the results in this table were 2w and 2x. The excellent selectivity was achieved on the benzylic position only and the aliphatic alcohols were not disturbed [17].

After substrate spectrum evaluation, control experiments were carried out to investigate the actual rule of the reaction factors and investigate the reaction mechanism (Table 3). Taking benzyl alcohol 1a as substrate, there was no formation of the product in the absence of light (Table 3, Entry 2), photocatalyst (Table 3, Entry 4), or under Ar atmosphere (Table 3, Entry 3). Otherwise, benzaldehyde could be detected without quinuclidine, which indicated the redox cycle was accelerated by quinuclidine (Table 3, Entry 5). Then the effect of different quenchers on the reaction was examined. When butylated hydroxytoluene (BHT) (3 eq) was added into the mixture of reactants as a radical scavenger, the yield dropped sharply to 10% (Table 3, Entry 6). Using sodium azide as a singlet oxygen scavenger, the monitored yield has also dropped dramatically (Table 3, Entry 7). Meanwhile, benzoguinone as a superoxide radical anion scavenger also inhibited the reaction (Table 3, Entry 8). Furthermore, the addition of CuCl₂ hindered the process of reaction (Table 3, Entry 9). The above results indicated there was a radical process involving single electron transfer and hydrogen atom transfer in this photoredox system.

To further investigate the reaction mechanism, we carried out the oxidation of deuterium-labelled 1-indanol 1k' under standard

Air

02

88

95

Table 2

Substrate scope for the oxidation of benzylic primary and secondary alcohols.^a



^aReaction condition: alcohol (0.2 mmol), 4CzIPN (3 mol%), quinuclidine (10 mol%), Bu₄NH₂PO₄ (25 mol%), MS (200 mg), MeCN (1 mL), DMSO (0.1 mL), Air (balloon), room temperature (rt), under 8 W blue LEDs irradiation. All are isolated yields except **2a** and **2p**.

^bIn presence of O₂ (balloon).

^cProlonged the reaction time to 15 h.

^dProlonged the reaction time to 20 h, and without Bu₄NH₂PO₄.

conditions (Scheme 2). The K_H/K_D value of 1.4 in the kinetic isotope effect experiment uncovered that C—H bond cleavage was the ratedetermining step. Thereafter, the Stern–Volmer fluorescence quenching experiments was investigated. The fluorescence intensity of 4CzlPN was quenched dramatically by quinuclidine and O_2 instead of benzyl alcohol (Table 4 and Figs. S2-4), revealed that the excited 4CzlPN did not interact directly with benzyl alcohol, but with quinuclidine and oxygen.

Based on all the mechanistic study above, we proposed a plausible mechanism in Scheme 3. Irradiation of photocatalyst 4CzIPN with blue LEDs generated the excited PC* ($E_{1/2}^{red}$ [PC*/PC⁻] = 1.35 V vs SCE) [18], which is sufficient for the oxidation of quinuclidine ($E_{1/2}^{ox}$ = 1.1 V vs SCE) [14g] to its radical cation. Singlet oxygen ¹O₂ was also generated through an energy transfer process between O₂ and excited PC* at the same time [2b,19]. Then a HAT process happened between the benzyl alcohol **1a** and quinuclidine radical cation to yield the α -hydroxy radical **I**. Meanwhile, the reduced form of the photocatalyst PC⁻ ($E_{1/2}^{ox}$ [PC/PC⁻] = 1.21 V vs SCE) [18] reduced ¹O₂ ($E_{1/2}^{red}$ [¹O₂/O₂⁻] = 0.65 V vs SCE) [20] to superoxide radical anion O₂⁻ which integrates with **I** to produce interme-

Table 3

Control experiments for the photochemical oxidation of benzyl alcohol.^a

	OH H 1a	4CzIPN quinuclidine Bu ₄ NH ₂ PO ₄ ,MS MeCN/DMSO rt,10h,blue LEDs 2a	
Entry	Controlled parameter	Notes	Yield (%)
1	Standard conditions		88
2	No light		0
3	Ar atmosphere		0
4	No PC		0
5	No quinuclidine		10
6	BHT (3 eq)	Radical scavenger	10
7	NaN_3 (1 eq)	Singlet oxygen scavenger	54
8	Benzoquinone (1 eq)	Superoxide radical anion scavenger	5
9	$CuCl_2$ (1 eq)	Electron scavenger	4

^a Reaction condition: benzyl alcohol (0.2 mmol), 4CzIPN (3 mol%), quinuclidine (10 mol%), $Bu_4NH_2PO_4$ (25 mol%), MS (200 mg), MeCN (1 mL), DMSO (0.1 mL), Air (balloon), room temperature (rt), under 8 W blue LEDs irradiation, yields were determined by GC using *n*-dodecane as an internal standard.



Scheme 2. Kinetic isotope effect (KIE) experiment.

 Table 4

 Fluorescence quenching experiments.



diate II. Finally, a protonation and elimination of the intermediate II delivered the final product 2a and H_2O_2 .

In conclusion, we have developed a green and robust method for the oxidation of benzylic primary and secondary alcohols with good functional group tolerance. Notably, our oxidation strategy has shown advanced benefit for the substrates that bearing a space-hindered *ortho*-substitute and good selectivity on the benzylic alcohols over aliphatic alcohols. Detailed mechanistic research revealed a quinuclidine mediated HAT process and blue LED promoted photoredox cycle was involved in our oxidation. This method represents a powerful example of the photoredox transformation and can be a beneficial supplement to the alcohol oxidation arsenal.



Scheme 3. Proposed mechanism.

Declaration of Competing Interest

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.

Acknowledgments

Financial support was provided by NSFC (21602185, 21772074), the Natural Science Foundation of Department of Science & Technology of Gansu Province (18JR3RA273), and Fundamental Research Funds for Central Universities (No. lzu-jbky-2018-42).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152878.

References

- [1] G. Tojo, Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice, Springer Science, New York, 2006.
- [2] (a) Y. Nosaka, A.Y. Nosaka, Chem. Rev. 117 (2017) 11302;
 - (b) A.A. Ghogare, A. Greer, Chem. Rev. 116 (2016) 9994.

- [3] (a) Y.Z. Chen, Z.U. Wang, H. Wang, J. Lu, S.H. Yu, H.L. Jiang, J. Am. Chem. Soc. 139 (2017) 2035:
 - (b) B. Zhang, J. Li, Y. Gao, R. Chong, Z. Wang, L. Guo, X. Zhang, C. Li, J. Catal. 345 (2017) 96.
- [4] (a) Q. Wang, M. Zhang, C. Chen, W. Ma, J. Zhao, Angew. Chem. Int. Ed. 49 (2010) 7976;
 - (b) S. Furukawa, T. Shishido, K. Teramura, T. Tanaka, ACS Catal. 2 (2011) 175; (c) M.J. Pavan, H. Fridman, G. Segalovich, A.I. Shames, N.G. Lemcoff, T. Mokari, ChemCatChem 10 (2018) 2541;
- (d) M. Zhang, C. Chen, W. Ma, J. Zhao, Angew. Chem. Int. Ed. 47 (2008) 9730; (e) R. Vadakkekara, A.K. Biswas, T. Sahoo, P. Pal, B. Ganguly, S.C. Ghosh, A.B. Panda, Chem. Asian J. 11 (2016) 3084.
- [5] (a) C. Meng, K. Yang, X. Fu, R. Yuan, ACS Catal. 5 (2015) 3760; (b) Y. Sugano, Y. Shiraishi, D. Tsukamoto, S. Ichikawa, S. Tanaka, T. Hirai, Angew. Chem. Int. Ed. 52 (2013) 5295;
- (c) R. Negishi, S.-I. Naya, H. Tada, J. Phys. Chem. C 119 (2015) 11771.
- [6] M. Rueping, C. Vila, A. Szadkowska, R.M. Koenigs, J. Fronert, ACS Catal. 2 (2012) 2810
- [7] A. Bhim, S. Sasmal, J. Gopalakrishnan, S. Natarajan, Chem. Asian J. 15 (2020) 3104.
- [8] A. Tanaka, K. Hashimoto, H. Kominami, J. Am. Chem. Soc. 134 (2012) 14526. Q. Xia, Z. Shi, J. Yuan, Q. Bian, Y. Xu, B. Liu, Y. Huang, X. Yang, H. Xu, Asian J. Org. [9] Chem. 8 (2019) 1933.
- [10] (a) R. Cibulka, R. Vasold, B. Konig, Chem - Eur. J. 10 (2004) 6224; (b) J. Zelenka, E. Svobodova, J. Tarabek, I. Hoskovcova, V. Boguschova, S. Bailly, M. Sikorski, J. Roithova, R. Cibulka, Org. Lett. 21 (2019) 114; (c) S. Fukuzumi, K. Yasui, T. Suenobu, K. Ohkubo, M. Fujitsuka, O. Ito, J. Phys. Chem. A 105 (2001) 10501; (d) K.A. Korvinson, G.N. Hargenrader, J. Stevanovic, Y. Xie, J. Joseph, V. Maslak, C.M. Hadad, K.D. Glusac, J. Phys. Chem. A 120 (2016) 7294; (e) P. Dongare, I. MacKenzie, D. Wang, D.A. Nicewicz, T.J. Meyer, Proc. Natl. Acad. Sci. U.S.A. 114 (2017) 9279; (f) B. Muhldorf, R. Wolf, Chem. Commun. 51 (2015) 8425; (g) M. Obst, B. Konig, Beilstein J. Org. Chem. 12 (2016) 2358. [11] S. Sheriff Shah, N. Pradeep Singh, D, Tetrahedron Lett. 59 (2018) 247. Schilling, D. Riemer, Y. Zhang, N. Hatami, S. Das, ACS Catal. 8 (2018) 5425.
 N.F. Nikitas, D.I. Tzaras, I. Triandafillidi, C.G. Kokotos, Green Chem. 22 (2020)
- 471.
- [14] (a) For recent reviews, see: L. Capaldo, D. Ravelli Eur. J. Org. Chem. 2017 (2017) 2056: (b) M.H. Shaw, J. Twilton, D.W. MacMillan, J. Org. Chem. 81 (2016) 6898; (c), For selected examples, see.X. Zhang, D.W.C. MacMillan J. Am. Chem. Soc. 139 (2017) 11353; (d) C. Le, Y. Liang, R.W. Evans, X. Li, D.W.C. MacMillan, Nature 547 (2017) 79; (e) X.-Q. Hu, J.-R. Chen, W.-J. Xiao, Chem 4 (2018) 2274; (f) J. Twilton, M. Christensen, D.A. DiRocco, R.T. Ruck, I.W. Davies, D.W.C. MacMillan, Angew. Chem. Int. Ed. 57 (2018) 5369; (g) J. Ye, I. Kalvet, F. Schoenebeck, T. Rovis, Nat. Chem. 10 (2018) 1037;
 - (h) V. Dimakos, H.Y. Su, G.E. Garrett, M.S. Taylor, J. Am. Chem. Soc. 141 (2019) 5149; (i) K. Guo, Z. Zhang, A. Li, Y. Li, J. Huang, Z. Yang, Angew. Chem. Int. Ed. 59
 - (2020) 11660.
- [15] J.L. Jeffrey, J.A. Terrett, D.W.C. MacMillan, Science 349 (2015) 1532.
- [16] Y. Wang, H.M. Carder, A.E. Wendlandt, Nature 578 (2020) 403.
- [17] J.B. Arterburn, Tetrahedron 57 (2001) 9765.
- [18] T.Y. Shang, L.H. Lu, Z. Cao, Y. Liu, W.M. He, B. Yu, Chem. Commun. 55 (2019) 5408.
- [19] C. Schweitzer, R. Schmidt, Chem. Rev. 103 (2003) 1685.
- [20] Katerina Krumova and Gonzalo Cosa, Chapter 1: Overview of Reactive Oxygen Species, in Singlet Oxygen: Applications in Biosciences and Nanosciences, Volume 1, 2016, pp. 1-21.