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Visible Light Mediated Chemo-selective Oxidation of Benzylic Alcohols

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ABSTRACT

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1. Introduction

Unarguably the synthesis of carbonyl compounds from alcohols represents one of the most addressed problems in organic synthesis as well as in process and medicinal chemistry. They serve as fundamental intermediates to the construction of a wide variety natural products as well as bioactive molecules.¹ Owing to their importance myriad methods have appeared for their synthesis particularly via oxidation of alcohols.² Though, the oxidation of alcohols in general is a very well addressed problem, however chemo-selective oxidation of alcohols,³ particularly benzyl and allyl alcohol still represents an interesting DDQ/NaNO₂,⁴ challenge. Though methods like DDQ/(MnOAc)₃,⁵ NBS/thiourea,⁶ vanadium complexes,⁷ K₂[OsO₂(OH)₄]/chloramine-T⁸ have been developed in recent years, however, most of these processes employ toxic metal catalysts and require higher temperatures.

Recently, considerable attention has been focussed towards visible light mediated strategies for the oxidation of alcohols.⁹ However, the disadvantage with most of these methods is lack of chemo-selectivity, use of complex or toxic catalytic system and high energy light source, that is, either 400 W metal halide, halide lamp or mercury lamp making them non-ideal for upscaling and industrial applications. For example to evade the use of high energy source, a LED/CFL mediated oxidation of alcohol was reported, which required a rather complex catalytic system comprising of riboflavin tetraacetate and non-heme iron catalyst¹⁰ and lacked selectivity. To overcome the issue of selectivity a well known DDQ/NaNO₂¹¹ catalytic system was used for chemo-selective oxidation of ally/benzyl alcohol.

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However, the limiting factor of this work is use of 400W metal halide lamp or solar light and use of DDQ, which has a LD50 of 82mg/Kg,¹² release of HCN as a by-product and requires molecular oxygen as well. This limitation to some extent were overcome in a recent visible light mediated report for selective oxidation of benzyl alcohols into benzaldehyde, wherein, the reaction is catalysed by use of CuCl₂ or Pt/TiO₂ in presence of molecular oxygen as an oxidant leading to the formation of

visible light responsive complex of Cu(II) with solvent

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Chemo-selective photocatalytic approaches

(acetonitrile or acetone).

A highly chemoselective visible light mediated strategy has been developed for oxidation of

benzylic alcohols. The method circumvents the use of toxic metal catalysts, high energy light source and operates at room temperature. Furthermore reaction is easily scalable to gram levels.



The preceding discussion makes it clear that development of a chemo-selective, metal free protocol employing use of a simple visible light source viz., LED or CFL is highly challenging and desirable. In this regard, Eosin Y, a commercially friendly

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organic dye has found tremendous applications in photoredox reactions like C-H functionalization, alkylation, arylation, cross dehydrogenative couplings.¹³ Thus, in continuation of our interest, ¹⁴ particularly towards photoredox catalysis, herein, we report a simple metal free catalytic system comprising of EOSIN-Y/TBHP for chemo-selective oxidation of benzylic alcohols. The method circumvents the use of high energy light source, metals as well as toxic side products. Furthermore, the method can easily be scaled to gram levels.

Table 1. Optimization of the reaction conditions*

		OH Eosin Y (mol % oxidant	ó), → 〔		
1a solvent				2a	
entry	EosinY (mol%)	light source	ТВНР	Solvent	Yield [%]**
			(equiv.)		
1	5	CFL (27 W)	1	ACN	55
2	5	Blue LEDs (455 nm)	1	ACN	65
3	5	Green LEDs (530 nm)	1	ACN	61
4	5	No Light	1	ACN	-
5	-	Blue LEDs	1	ACN	trace
6	5	Blue LEDs	-	ACN	-
7	5	Blue LEDs	2	ACN	70
8	5	Blue LEDs	3	ACN	88
9	10	Blue LEDs	3	ACN	90
10	3	Blue LEDs	3	80	75
11	5	Blue LEDs	3	DMSO	-
12	5	Blue LEDs	3	DMF	-
13	5	Blue LEDs	3	MeOH	-
14	5	Blue LEDs	3 ^b	CAN	-
15	5	Blue LEDs	3°	ACN	-

*Reactants: 1 (1 mmol), solvent (3ml), $4A^{\circ}MS 3 wt\%$ for 48 h at rt. ${}^{b}H_{2}O_{2}$ and ${}^{\circ}Benzoyl peroxide were used instead of TBHP. **Isolated yields$

We started with the use of 1-phenyl ethanol as model substrate, 27 W household CFL as light source and Eosin Y (5 mol%) as photocatalyst in presence of 1 equiv. of TBHP as an oxidant using ACN as solvent. To our delight, the reaction resulted in the synthesis of acetophenone in 55% yield after 32 h (table 1 entry 1). We further screened various light sources, wherein, the use of LED resulted in an improvement of yields with blue LED as the most suitable (table entry 2-3). Furthermore, there was no reaction in the absence of either light, Eosin Y or TBHP (table entry 4-6). It would be pertinent to mention here that reaction can easily be switched on and off by turning on and off the light source. On increasing the amount of TBHP to 2 and 3 equiv., the reaction yields improved to 70 and 88% respectively (table 1, entry 7-8). The studies also warranted optimization of catalyst loading, an increase of catalyst loading to 10 mol % didn't result in significant enhancement in yields, however, decreasing it to 3 % resulted in drop of yields (table 1 entry 9-10). Additionally, we could only get the product in trace amounts in other solvents such as DMSO, DMF and MeOH (Table 1, entries 11-13). The reaction without any oxidant and in presence of other oxidants viz., H₂O₂ and benzoyl peroxide, resulted in no product formation (Table 1, entries 14-15).



Scheme 2. Substrate scope with secondary alcohols. Isolated yields

Having conditions optimized,¹⁶ we considered expanding the generality of the reaction to diverse α -arylated ethanols (Scheme 2). The reactions of halo substituted phenyl ethanols i.e., 4bromo, 4-chloro, 2-chloro 1-phenyl ethanol gave corresponding products (2b-d) in good yields. The reaction of 4-methoxy, 2methoxy and 2,4-dimethoxy 1-phenyl ethanol also proceeded efficiently giving corresponding carbonyls (2e-g) in excellent yields and comparatively shorter reaction times. The effect of withdrawing groups on aryl was also investigated on present reaction system, using 3-nitro and 2-trifluoromethyl 1-phenyl ethanol as substrates to get products 2h-i in 62 and 72% yields. We also explored the scope feasibility of reaction to bicyclic system such as 1-naphthyl ethanol to get 2j in 78% yields. The scope of reaction was also extended to various heterocylcilc alcohols 3-pyridyl and 2-pyridyl ethanol. However, the reaction gave the corresponding products 2k-l in 25 and 20% yields respectively, and took comparatively larger times to complete. The reaction under optimized conditions also gave corresponding product 2m-n from 1-phenyl propanol and diphenyl methanol in 88 and 96% yields respectively. We also extended substrate scope to fluorenol and 2,7-dibromo fluorenol to get corresponding carbonyls in 20-p in good yields. To unequivocally establish the selectivity of our method we carried

out the reaction with cyclohexanone and 2,6-diemthyl cyclohexanone which as expected didn't give any product formation.



Scheme 3. Substrate scope with benzyl alcohols. Isolated yields

We were further intrigued to examine the scope of present reaction system on benzyl alcohols (Scheme 3). Generally, in all the cases benzaldehydes were obtained in good to excellent yields, however, in some cases we observed the formation of corresponding benzoic acids in trace amounts. It would be pertinent to mention here that we tried to expand the reaction system for synthesis of benzoic acids, however, even after the increasing the amount of TBHP to 10 equiv., the benzoic acid was formed in trace amounts (<10%). Importantly the benzoic acids can easily be removed during work up with sod. bicarbonate. Initially we started with the reaction of benzyl alcohol under optimized conditions, which as expected gave benzaldehyde (4a) in 60% yields. The reaction of 4-methoxy, 2,4-dimethoxy and 2,4,5-trimethoxy benzyl alcohol also gave corresponding product 4b-d in excellent yields. Likewise 4chloro and 2-chloro benzyl alcohol also gave corresponding aldehydes in good yields (4e-f). The reaction with 3-nitro and 4nitro benzyl alcohols also proceeded efficiently to give corresponding products 4g-h in 75 and 72% yields respectively. Furthermore, 2-napthyl methanol and allylic alcohol (cinnamyl alcohol) also gave aldehydes 4i-j in 89 and 72% yields respectively. The reaction was also found extendable to heterocyclic alcohols to give corresponding products, 4k-m in 67, 64 and 60% yields respectively. The reaction with non-benzyl

alcohols viz., 2-phenyl ethanol and octanol to our expectation didn't result in any product formation even after 72h.

To unambiguously ascertain the chemo-selectivity of our reaction system we examined the competitive oxidation of two different alcohols (Scheme 4). The reaction of 1,3 diols i.e., 1-phenylbutane-1,3-diol and 1-(4-methoxyphenyl)butane-1,3-diol to our delight lead to the exclusive formation of 3-hydroxy-1-phenylbutan-1-one and 3-hydroxy-1-(4-methoxyphenyl)butan-1-one (**6a-b**)) in 72 and 85% yields respectively (Eq. 1). Furthermore, we explored the chemoselective oxidation of a mixture of 1-phenyl ethanol and 2-phenyl ethanol (Eq. 2) and 2-phenyl ethanol and benzyl alcohol (Eq. 3) resulting in complete oxidation of 1-phenyl ethanol and benzyl alcohol, with no product formation from 2-phenyl ethanol.



Scheme 4. Chemoselectivity in different alcohols

We were further intrigued to see if the reaction under optimized conditions can be used for gram scale synthesis of carbonyl compounds, which would as it turns out demonstrate its practical utility. Thus, we carried out the reaction with 1-phenyl propanol (1g, 1 equiv.) to afford propiophenone **2m** in 85% (837 mg) yields (scheme 5).



Scheme 5. Gram scale oxidation of 1-phenyl propanol

A possible explanation of the reaction is claeavge of TBHP by photo-excited Eosin Y*,¹⁵ leading to the generation of *tert*-butoxy radical (*t*-BuO') and hydroxyl radical (OH') The *t*-BuO' radical then abstracts hydrogen from benzylic position to give benzylic radical, which on subsequent loss of water molecule aided by the OH' results in the generation of corresponding carbonyl compounds (scheme 6).



Scheme 6. Plausible mechanism

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In conclusion we have developed a highly chemoselective photocatalytic strategy for oxidation of benzylic/allylic alcohols to corresponding carbonyls. Cheap and easily available catalytic system comprising of Eosin Y and TBHP was used. The method not only obviates the use of toxic metal catalysts, but also high energy light sources. The reaction is easily extendable to primary as well as secondary benzyl alcohols having diverse set of electron withdrawing as well as donating functions at room temperature maintaining high selectivity. Furthermore, the reaction can easily be upscaled to gram levels.

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References and notes

- a) Passiniemi, M.; Koskinen, A. M. Beilstein J. Org. Chem. 2013, 9, 2641-2659; (b) Baumann, M.; Baxendale, I. R. Beilstein J. Org. Chem. 2013, 9, 2265-2319. (c) Ma, Y.-T.; Fan, H.-F.; Gao, Y.-Q.; Li, H.; Zhang, A.-L.; Gao, J.-M. Chem. Biol. Drug Des. 2013, 81, 545-552; (d) Brown, P. D.; Willis, A. C.; Sherburn, M. S.; Lawrence, A. L. Org. Lett. 2012, 14, 4537-4539; (e) Kouloura, E.; Halabalaki, M.; Lallemand, M.-C.; Nam, S.; Jove, R.; Litaudon, M.; Awang, K.; Hadi, H. A.; Skaltsounis, A.-L. J. Nat. Prod. 2012, 75, 1270-1276; (f) Chen, J.-J.; Cho, J.-Y.; Hwang, T.-L.; Chen, I.-S. J. Nat. Prod. 2008, 71, 71-75; (g) Su, C.-R.; Kuo, P.-C.; Wang, M.-L.; Liou, M.-J.; Damu, A. G.; Wu, T.-S. J. Nat. Prod. 2003, 66, 990-993; (h) Lin, L.-C.; Chou, C.-J.; Chen, K.-T.; Chen, C.-F. J. Nat. Prod. 1993, 56, 926-928.
- a) Chen, B.; Wang, L.; Gao, S. ACS Catal. 2015, 5, 5851-5876;
 (b) Hoover, J. M.; Steves, J. E.; Stahl, S. S. Nat. Protocols 2012, 7, 1161-1166;
 (c) Parmeggiani, C.; Cardona, F. Green Chem. 2012, 14, 547-564;
 (d) Zhan, B.-Z.; Thompson, A. Tetrahedron 2004, 60, 2917-2935;
 (e) Matsumoto, T.; Ueno, M.; Wang, N.; Kobayashi, S. Chem. Asian J. 2008, 3, 196-214;
 (f) Mallat, T.; Baiker, A. Chem. Rev. 2004, 104, 3037-3058.
- a) Manzini, S., Urbina-Blanco, C. S. A.; Nolan, S. P. Organometallics 2013, 32, 660-664; (b) Hoover, J. M.; Stahl, S. S. J. Am. Chem. Soc. 2011, 133, 16901-16910; (b) De Luca, L.; Giacomelli, G.; Porcheddu, A. Org. Lett. 2001, 3, 3041-3043; (d) Adam, W.; Hajra, S.; Herderich, M.; Saha-Moller, C. R. Org. Lett. 2000, 2, 2773-2776.
- 4. Wang, L.; Li, J.; Yang, H.; Lv, Y.; Gao, S. J Org Chem. 2012 77, 790-794.
- Cosner, C. C., Cabrera, P. J.; Byrd, K. M.; Thomas, A. M.; Helquist, P. Org. Lett. 2011, 13, 2071-2073.
- 6. [6] Tripathi, C. B.; Mukherjee, S. J. Org. Chem. 2012, 77, 1592-1598.
- a) Rout, L.; Nath, P.; Punniyamurthy, T. Adv. Synth. Catal. 2007, 349, 846-848; (b) Hanson, S. K.; Wu, R.; pete Silks; L. A. Org. Lett., 2011, 13, 1908-1911.
- Devari, S.; Deshidi, R.; Kumar, M.; Kumar, A.; Sharma, S.; Rizvi, M.; Kushwaha, M.; Gupta, A. P.; B. A. Shah, *Tetrahedron Lett.* 2013, 54, 6407-6410.

- a) Meng, C.; Yang, K.; u, X.; Yuan, F. R. ACS Catal. 2015, 5, 3760-3766; (b) Abedi, S.; Morsali, A. ACS Catal. 2014, 4, 1398-1403; (c) Lang, X.; Ma, W.; Chen, C.; Ji, H.; Zhao, J. Acc. Chem. Res. 2014, 47, 355-363; (d) Zhang, M.; Wang, Q.; Chen, C.; Zang, L.; Ma, W.; Zhao, J. Angew. Chem. Int. Ed. 2009, 48, 6081-6084.
- 10. Muhldorf, B.; Wolf, R. Angew. Chem. Int. Ed. Engl. 2016, 55, 427-430.
- 11. Walsh, K.; Sneddon, H. F.; Moody, C. J. Org. Lett. 2014, 16, 5224-5227.
- Adams, J. P.; Alder, C. M.; Andrews, I.; Bullion, A. M.; Campbell-Crawford, M.; Darcy, M. G.; Hayler, J. D.; Henderson, R. K.; Oare, C. A.; Pendrak, I.; Redman, A. M.; Shuster, L. E.; Sneddon, H. F.; Walker, M. D. *Green Chem.* **2013**, *15*, 1542-1549.
- (a) Hari, D. P.; Schroll, P.; Konig, B. J. Am. Chem. Soc. 2012, 134, 2958-2961; (b) Hari, D. P.; Konig, B. Chem. Commun. 2014, 50, 6688-6699; (c) Zhong, J.-J.; Meng, Q.-Y.; Liu, B.; Li, X.-B.; Gao, X.-W.; Lei, T.; Wu, C.-J.; Li, Z.-J.; Tung, C.-H.; Wu, L.-Z. Org. Lett. 2014, 16, 1988-1991; (d) Majek, M.; Filace, F.; von Wangelin, A. J. Beilstein J. Org. Chem. 2014, 10, 981–989; (e) Meyer, A. U.; Slanina, T. Å.; Yao, C.-J.; Konig, B. ACS Catalysis 2016, 6, 369-375.
- a) Deshidi, R.; Kumar, M.; Devari, S. Shah, B. A. Chem. Commun. 2014, 50, 9533-9535; (b) Devari, S.; Kumar, M.; Deshidi, R.; Rizvi, M.; Shah, B. A. Beilstein J. Org. Chem. 2014, 10, 2649-2653; (c) Devari, S.; Kumar, A.; Deshidi, R.; Shah, B. A. Chem. Commun. 2015, 51, 5013-5016; (d) Deshidi, R.; Devari, S.; Shah, B. A. Org. Chem. Front. 2015, 2, 515; (e) Deshidi, R.; Devari, S.; Shah, B. A. Eur. J. Org. Chem. 2015, 1428-1432; (f) Kumar, M.; Devari, S.; Kumar, A.; Sultan, S.; Ahmed, Q. N.; Rizvi, M.; Shah, B. A. Asian J. Org. Chem., 2015, 4, 438-441; (g) Kumar, A.; Shah, B. A. Org. Lett. 2015, 17, 52325235; (h) Sultan, S.; Kumar, M.; Devari, S.; Mukherjee, D.; Shah, B. A. ChemCatChem 2016, 18, 703-707; (i) Devari, S.; Shah, B. A. Chem. Commun. 2016, 52, 1490-1493.
- a) Li, J.; Zhang, J.; Tan, H.; Wang, D. Z. Org. Lett. 2015, 17, 2522-2525; (b) Yang, W.; Yang, S.; Li, P.; Wang, L. Chem. Commun. 2015, 51, 7520-7523.
- 16. General procedure for oxidation of alcohols: Oven dried round bottom flask was charged with Eosin Y (5 mmol) alcohol (1 mmol) and 3 equiv. of TBHP (5.5M in decane) in dry ACN. The resulting mixture was degassed for 15 mins, followed by back filling N₂, and then irradiated under Blue LED light (12W, 455 nm) at room temperature (25 °C). After reaction completion monitored through TLC, the mixture was diluted with 15 ml of 10% NaHCO₃ solution, and extracted with EtOAc (3 × 20 ml). The combined organic extracts were washed with brine (20 ml), dried over Na₂SO₄, and concentrated on vacuo. Purification of the crude product on silica gel using EtOAc:Hexane as solvent system afforded the desired product.

Supplementary Material

Experimental procedure, characterization data, ¹H and ¹³C NMR of relevant compounds.

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Graphical Abstract



Highlights:

- Metal free •
- Visible light •
- Low catalyst loading •
- **Operationally easy** •
- Accepter