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# Oxidation of benzylic methylenes to ketones with Oxone–KBr in aqueous acetonitrile under transition metal free conditions

Lixia Yin, Jingjing Wu, Juan Xiao, Song Cao\*

Shanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

mechanism was also suggested.

# ARTICLE INFO

### ABSTRACT

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The oxidation of benzylic C-H bond is one of the most useful and fundamental transformations due to its wide variety of applications in the synthesis of pharmaceuticals and fine chemicals.<sup>1</sup> It is a powerful tool to generate high value chemicals from less expensive raw materials such as alkyl aromatics.<sup>2</sup> Up to now, numerous methods have been developed for the oxidation of benzylic methylenes into the corresponding ketones.<sup>3</sup> Traditionally, these benzylic oxidation reactions involve the use of stoichiometric amounts of metal oxidants, such as potassium permanganate, potassium dichromate. or cerium triflate.<sup>4</sup> During the last decades. great efforts have been made to improve these transformations with catalytic amount of transition metal complexes in combination with various environmentally benign oxidants like  $O_2$ ,  $H_2O_2$ , IBX, PhIO, and tert-butylhydroperoxide (TBHP) under homogeneous and heterogeneous conditions.<sup>5</sup> Although the present methods could successfully be used to convert alkylarenes to aromatic ketones, complicated, expensive, or toxic metal catalysts are required in most of these systems.<sup>6</sup> Therefore, there is a high demand for the development of clean and economical processes for the selective oxidation of alkylarenes to higher value added phenyl ketones with readily available, inexpensive, and non-toxic oxidants and catalysts.

On the other hand, as an efficient, cheap, versatile, and environmentally friendly oxidizing agent, Oxone(2KHSO<sub>5</sub>·KHSO<sub>4</sub>·K<sub>2</sub>SO<sub>4</sub>) has attracted increasing interest in organic synthesis in recent years.<sup>7</sup> It has found many applications in oxidation of amines, alcohols, aldehydes, and epoxidation of alkenes.<sup>8</sup> For example, in 2002,

\* Corresponding author. E-mail address: scao@ecust.edu.cn (S. Cao).

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sponding 1,2-*bis*-dialkylcyano hydrazines using Oxone–KBr in aqueous medium.<sup>9</sup> In 2006, Desai developed a simple and efficient method for the chemoselective dethioacetalization of dithioacetals to aldehydes and ketones using Oxone–KBr in aqueous acetonitrile at room temperature.<sup>10</sup> In 2009, Vinod described a novel approach to aromatic ketones by the oxidation of the corresponding alkylarenes using 2-iodobenzoic acid (2IBAcid) in combination with co-oxidant Oxone.<sup>11</sup> More recently, Yu reported the selective oxidation of sulfides to sulfoxides or sulfones by employing Oxone as oxidant without the utilization of any catalyst/additive.<sup>12</sup> In this Letter, we report a green and efficient approach for the oxidation of benzylic methylenes to their corresponding ketones with Oxone and KBr in aqueous acetonitrile (Scheme 1).

Desai prepared a series of azo-bis nitriles by oxidation of corre-

A green and highly efficient protocol for the oxidation of benzylic methylenes to their corresponding

ketones with a combination of Oxone and KBr in aqueous acetonitrile is developed. The H<sub>2</sub><sup>18</sup>O labeling

experiment demonstrated that the oxygen introduced into ketone originated from water. A plausible

In the course of studies on the synthesis of 1-bromo-4-isobutylbenzene **3** by the reaction of isobutylbenzene **1a** with NH<sub>4</sub>Br and Oxone in undried CH<sub>3</sub>CN according to the literature procedure,<sup>13</sup> we found the results were different and an unexpected oxidative product **2a** was observed in addition to small amount of the normal brominated product **3** (Scheme 2). Most of the starting material **1a** was recovered.



Scheme 1. Oxidation of benzylic methylenes by Oxone-KBr-CH<sub>3</sub>CN-H<sub>2</sub>O system.





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**Scheme 2.** Reaction of **1a** with  $NH_4Br$  in the presence of Oxone in  $CH_3CN$  (Note: acetonitrile and other solvents were purchased commercially and used without further drying, except those indicated in the Letter).

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Optimization of the reaction conditions

	PhCH <sub>2</sub> CH <sub>3</sub> -	Solvent, 45 °C	PhCOCH <sub>3</sub>	
Entry	Solvent (6 mL)	Bromide (1.1 equiv)	Oxone (equiv)	Yield <sup>a</sup> (%)
1	CH <sub>3</sub> CN	NH <sub>4</sub> Br	1.1	15
2	CH₃CN	NH <sub>4</sub> Br	2.2	29
3	CH₃CN	KBr	1.1	30
4	CH₃CN	KBr	2.2	50
5	DMSO	KBr	2.2	0
6	DMF	KBr	2.2	0
7	CH₃OH	KBr	2.2	7
8	CH <sub>3</sub> CN (dried)	KBr	2.2	0
9	CH <sub>3</sub> CN, H <sub>2</sub> O (0.1 mL)	KBr	2.2	44
10	CH <sub>3</sub> CN, H <sub>2</sub> O (0.5 mL)	KBr	2.2	79
11	CH <sub>3</sub> CN, H <sub>2</sub> O (1 mL)	KBr	2.2	68
12	CH <sub>3</sub> CN, H <sub>2</sub> O (2 mL)	KBr	2.2	35

<sup>a</sup> Yields were based on GC analysis.

Encouraged by this result, ethylbenzene **1b** was selected as representative reactant for optimization of the unexpected reaction conditions (Table 1). For our initial studies, efforts were directed toward the evaluation of the bromide in the oxidation reaction. It was found that KBr is more effective than  $NH_4Br$  (entries 1–4). Thus, we used KBr as bromine source in the following investigation.

The reaction was significantly affected by the solvent (Table 1, entries 4–7). Only acetonitrile afforded a moderate yield (entry 4, 50%) of the expected product **2b** and no oxidative product was observed in other solvents even after prolonged reaction time (entries 5–7). Usually, water plays an important role in the oxidation of benzylic methylenes to ketones.<sup>2b,c,8b,14</sup> Thus, the effect of the amount of water in the system on the conversion was examined by varying the amount of water in the presence of Oxone and KBr using CH<sub>3</sub>CN as solvent at 45 °C (entries 8–12). It was found that 0.5 mL of water was sufficient to carry out this reaction smoothly (entry 10). An increase in the amount of water to more than 1 or 2 mL led to a decrease of the yield of oxidative product (entries 11 and 12), furthermore the yield was reduced by decreas-

Table	2				
Effect	of amount	of Oxone on	the	oxidation	of 1b <sup>a</sup>

Entry	Oxone (equiv)	Yield <sup>b</sup> (%)
1	1.1	34
2	1.5	54
3	1.9	68
4	2.2	79
5	2.5	60

<sup>a</sup> Reaction conditions: CH<sub>3</sub>CN (6 mL), H<sub>2</sub>O (0.5 mL), KBr (1.1 equiv), 45 °C.

<sup>b</sup> Yields were based on GC analysis.

Table 3

ffect of amount of catalyst (KBr) on the formation of 2	2bª	
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Entry	KBr (equiv)	Time (h)	Yield <sup>b</sup> (%)
1	0.1	120	7
2	0.2	99	60
3	0.5	6	86
4	1.1	6	79
5	2.2	6	5

 $^a$  Reaction conditions: CH\_3CN (6 mL), H\_2O (0.5 mL), Oxone (2.2 equiv), 45 °C.  $^b$  Yields were based on GC analysis.

ing the amount of water to 0.1 mL (entry 9). When dried  $CH_3CN$  was used without the addition of water, no expected oxidative product **2b** was detected and most of ethylbenzene (**1b**) remained unconverted (entry 8).

The effect of amount of Oxone on the oxidation of **1b** was investigated (Table 2). The results indicated that 2.2 equiv Oxone afforded the oxidation product **2b** in good yield (entry 4). An increase in the amount of Oxone to 2.5 equiv showed no significant improvement in yield (entry 5), whereas the yield was reduced by decreasing the amount of Oxone (entries 1–3).

Using the same substrate **1b**, the effect of amount of KBr on the oxidation of **1b** was also examined (Table 3). To obtain a reasonable yield of **2b**, 0.5 equiv KBr had to be used (entry 3). Too little KBr would lead to incomplete conversion of **1b** (entries 1 and 2), whereas too much KBr would result in the formation of undesired bromination products (entries 4 and 5).

The yield of the oxidation product was also affected by the reaction temperature. The results are shown in Table 4. The reaction proceeded smoothly at 45 °C, yielding the expected product in 86% yield. However, decreasing the reaction temperature would lead to a decrease in yield, whereas a further increase in temperature showed no improvement in the yield (entries 4 and 5).

To investigate the generality and scope of the novel transition metal-free system, a range of structurally diverse hydrocarbons were examined under the optimized reaction conditions (Table 5).<sup>15</sup> Most benzylic methylenes could be successfully oxidized with this new Oxone-KBr-CH<sub>3</sub>CN-H<sub>2</sub>O system to give the corresponding ketones in high to excellent yields (entries 1-11). When 1,4diethylbenzene (1d), isochroman (1e), 1,3-dihydroisobenzofuran (1f), 1,2,3,4-tetrahydronaphthalene (1k) and indan (1l) were used as substrates, which have two -CH<sub>2</sub>- (methylene) groups attached to the benzene ring, only one benzyl group can be converted to a carbonyl group, and another methylene group cannot be oxidized even after more Oxone was added (entries 4-6, 11 and 12). 1,4-Diethylbenzene (1d) could not be directly oxidized to 1,1'-(1,4phenylene)diethanone (2g) in one pot, it was oxidized to 1-(4-ethylphenyl)ethanone (2d) in the first step. The 2d should be separated and purified, and then used as substrate (1g, 1-(4ethylphenyl)ethanone which is the same as 2d) to further oxidize to 1,1'-(1,4-phenylene)diethanone (2g).

Table 4						
Effect of reaction	temperature	on	the	oxidation	of	1b <sup>a</sup>

Entry	Temperature (°C)	Time (h)	Yield <sup>b</sup> (%)
1	0	48	30
2	25	18	70
3	35	6	82
4	45	4	86
5	65	2	85

<sup>a</sup> Reaction conditions: CH<sub>3</sub>CN (6 mL), H<sub>2</sub>O (0.5 mL), Oxone (2.2 equiv), KBr (1.1 equiv).

<sup>b</sup> Yields were based on GC analysis.

#### Table 5

The Oxone-I	KBr–CH₃CN–H₂	O system for	· benzylic	oxidation <sup>a</sup>
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 $^{a}$  Reaction conditions: CH\_3CN (6 mL), H\_2O (0.5 mL), Oxone (2.2 equiv), KBr (1.1 equiv).

<sup>b</sup> Yields were based on GC analysis.

When the oxygen atom is present in the ring adjacent to the benzylic position, such as isochroman (1e), 1,3-dihydroisobenzofuran (1f), the desired products, lactones (2e and 2f) were obtained in excellent yields. In the case of indan (1l), the reaction did not proceed smoothly and only 47% of 1-indanone (2l) was formed. Oxidation of dibenzyl ether (1m) did not afford the desired product but gave benzaldehyde (2m) in 67% yield along with 22% of benzoic acid (2n). When benzyl alcohol (1n) was subjected to oxidation with this novel system, benzoic acid (2n) was exclusively obtained in 81% yield with no formation of benzaldehyde. It is indicated that benzyl alcohol is more easily oxidized. Interestingly, oxidation of toluene (1o) provided benzyl bromide (2o) as the only product formed under these reaction conditions and no oxidized products were observed. However, substrates bearing a strongly



Scheme 3. An isotopic labeling investigation of the mechanism of the oxidation.



Scheme 4. A plausible mechanism for the oxidation.

electron-withdrawing group on the ethylbenzene ring (**1p**) disfavored benzylic oxidation and bromination of benzyl group proceeded smoothly, and **2p** was obtained in high yield. If a strong electron-donating group such as CH<sub>3</sub>O was present on the aromatic ring, the aromatic ring bromination occurred and afforded **2q** in high yield.

To explain the mechanism of the oxidation reaction, several additional experiments were conducted using **1b** as a substrate under the optimized reaction conditions. When the reaction was carried out under an argon atmosphere, the reaction proceeded smoothly and afforded **2b** in good yield. It is indicated that oxygen in the air has no influence on the formation of **2b**. If the reaction was performed under dark conditions, almost no oxidative product **2b** could be detected and aromatic ring bromination obtained instead of benzylic C–H oxidation. In addition, no reaction was observed in the absence of water or KBr.

In order to further probe the origin of oxygen in ketone, the <sup>18</sup>Olabeling experiment was also performed under the optimized reaction conditions (Scheme 3). When H<sub>2</sub><sup>18</sup>O was added to the reaction, <sup>18</sup>O was incorporated into acetophenone. The ratio of **2b** and <sup>18</sup>Olabeled acetophenone **2b**' was 1:2. The <sup>18</sup>O labeled water experiment clearly demonstrated that oxygen introduced into ketone originated from water.

Finally, a possible mechanism for the oxidation of benzylic methylenes (**I**) to ketones (**IV**) with Oxone–KBr–CH<sub>3</sub>CN–H<sub>2</sub>O system is depicted in Scheme 4. Initially, potassium bromide reacts with Oxone to produce molecular bromine. Homolytic cleavage of bromine under visible light irradiation generates the bromine radical. This reactive intermediate initiates benzylic hydrogen abstraction leading to the formation of the stable benzyl bromide intermediate (**II**), which undergoes hydrolysis to give the corresponding alcohol (**III**). The benzylic alcohol is further oxidized by the second molecule of Oxone to give ketone.<sup>2b,3e,5b</sup>

In summary, we reported a novel and practical approach for the oxidation of benzylic methylenes to the corresponding ketones with novel Oxone–KBr–CH<sub>3</sub>CN–H<sub>2</sub>O system. The  $H_2^{18}$ O labeling experiment demonstrated that the oxygen atom incorporated into ketone is derived from water.<sup>16</sup>

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# Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012. 06.036.

## **References and notes**

- (a) Godula, K.; Sames, D. Science 2006, 312, 67; (b) Li, X.-H.; Chen, J.-S.; Wang, X.-C.; Sun, J. -H.; Antonietti, M. J. Am. Chem. Soc. 2011, 133, 8074; (c) Ni, L.-L.; Ni, J.; Lv, Y.; Yang, P.; Cao, Y. Chem. Commun. 2009, 2171; (d) Kesavan, L.; Tiruvalam, R.; Ab Rahim, M. H.; bin Saiman, M. I.; Enache, D. I.; Jenkins, R. L; Dimitratos, N.; Lopez-Sanchez, J. A.; Taylor, S. H.; Knight, D. W.; Kiely, C. J.; Hutchings, G. J. Science 2011, 331, 195; (e) Xia, J.-B.; Cormier, K. W.; Chen, C. Chemical Science, 2012, online, DOI: http://dx.doi.org/10.1039/c2sc20178j.
- (a) Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D. A.; Oldham, J.; Burton, A. J.; Barrett, A. G. M. Org. Lett. 2005, 7, 4549; (b) Dohi, T.; Takenaga, N.; Goto, A.; Fujioka, H.; Kita, Y. J. Org. Chem. 2008, 73, 7365; (c) Yi, C. S.; Kwon, K.-H.; Lee, D. W. Org. Lett. 2009, 11, 1567.
- (a) Wang, J.-Q.; He, L.-N. New J. Chem. 2009, 33, 1637; (b) Li, H.-R.; Li, Z. –P.; Shi, Z.-J. Tetrahedron 2009, 65, 1856; (c) Zhang, J.-T.; Wang, Z.-T.; Wang, Y.; Wan, C.-F.; Zheng, X.-Q.; Wang, Z.-Y. Green Chem. 2009, 11, 1973; (d) Kumar, R. A.; Maheswari, C. U.; Ghantasala, S.; Jyothi, C.; Reddya, K. R. Adv. Synth. Catal. 2011, 353, 401; (e) Tada, N.; Ban, K.; Hirashima, S.; Itoh, A. Org. Biomol. Chem. 2010, 8, 4701.
- (a) Shaabani, A.; Mirzaei, P.; Naderia, S.; Lee, D. G. *Tetrahedron* **2004**, 60, 11415;
  (b) Mohammadpoor-Baltork, I.; Sadeghi, M. M.; Adibi, A. H. *Molecules* **2001**, 6, 900;
  (c) Laali, K. K.; Herbert, M.; Cushnyr, B.; Bhatt, A.; Terrano, D. *J. Chem. Soc., Perkin Trans.* 1 **2001**, 578.
- (a) Dapurkar, S. E.; Kawanami, H.; Yokoyama, T.; Ikushima, Y. *Catal. Commun.* 2009, *10*, 1025; (b) Khan, A. T.; Parvin, T.; Choudhury, L. H.; Ghosh, S. *Tetrahedron Lett.* 2007, *48*, 2271; (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. J. *Am. Chem. Soc.* 2001, *123*, 3183; (d) Lee, N. H.; Byun, J. C.; Oh, T.-H. *Bull. Korean Chem. Soc.* 2005, *26*, 454; (e) Zhu, M.-X.; Wei, X.; Li, B.-D.; Yuan, Y.-Z. *Tetrahedron Lett.* 2007, *48*, 9108.
- (a) Mohapatra, S. K.; Selvam, P. J. Catal. 2007, 249, 394; (b) Singh, S. J.; Jayaram, R. V. Catal. Commun. 2009, 10, 2004; (c) Vanover, E.; Huang, Y.; Xu, L.-B.; Newcomb, M.; Zhang, R. Org. Lett. 2010, 12, 2246; (d) Aguadero, A.; Falcon, H.;

Campos-Martin, J. M.; Al-Zahrani, S. M.; Fierro, J. L. G.; Alonso, J. A. Angew. Chem., Int. Ed. 2011, 50, 6557.

- (a) Hull, J. F.; Balcells, D.; Sauer, E. L. O.; Raynaud, C.; Brudvig, G. W.; Crabtree, R. H.; Eisenstein, O. J. Am. Chem. Soc. 2010, 132, 7605; (b) Yusubov, M. S.; Nemykin, V. N.; Zhdankin, V. V. Tetrahedron 2010, 66, 5745; (c) Thottumkara, P. P.; Vinod, T. K. Org. Lett. 2010, 12, 5640; (d) Liu, P.; Liu, Y.-G.; Wong, E. L.; Xiang, S.; Che, C.-M. Chem. Sci. 2011, 2, 2187.
- (a) Gella, C.; Ferrer, E.; Alibés, R.; Busqué, F.; de March, P.; Figueredo, M.; Font, J. J. Org. Chem. 2009, 74, 6365; (b) Yusubov, M. S.; Zagulyaeva, A. A.; Zhdankin, V. V. Chem. Eur. J. 2009, 15, 11091; (c) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. Org. Lett. 2003, 5, 1031.
- Tamhankar, B. V.; Desai, U. V.; Mane, R. B.; Kulkarni, P. P.; Wadgaonkar, P. P. Synth. Commun. 2002, 32, 3643.
- Desai, U. V.; Pore, D. M.; Tamhankar, B. V.; Jadhav, S. A.; Wadgaonkar, P. P. Tetrahedron Lett. 2006, 47, 8559.
- Ojha, L. R.; Kudugunti, S.; Maddukuri, P. P.; Kommareddy, A.; Gunna, M. R.; Dokuparthi, P.; Gottam, H. B.; Botha, K. K.; Parapati, D. R.; Vinod, T. K. Synlett 2009, 1, 117.
- 12. Yu, B.; Liu, A.-H.; He, L.-N.; Li, B.; Diao, Z.-F.; Li, Y.-N. Green Chem. 2012, 14, 957.
- (a) Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. Synth. Commun. 2002, 32, 279; (b) Kumar, M. A.; Rohitha, C. N.; Kulkarni, S. J.; Narender, N. Synthesis 2010, 10, 1629.
- (a) Lee, Y.-M.; Dhuri, S. N.; Sawant, S. C.; Cho, J.; Kubo, M.; Ogura, T.; Fukuzumi, S.; Nam, W. Angew. Chem., Int. Ed. 2009, 48, 1803; (b) Zhou, M.; Schley, N. D.; Crabtree, R. H. J. Am. Chem. Soc. 2010, 132, 12550.
- 15. General procedure of the oxidation reactions: To a solution of aromatic compound (1 mmol) in CH<sub>3</sub>CN (6 mL) and H<sub>2</sub>O (0.5 mL) were added KBr (0.5 mmol) and Oxone (2.2 mmol), and the mixture was stirred at 45 °C. After completion (monitored by TLC), the reaction mixture was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography using hexane/ethyl acetate as eluent (20–80: 1).
- 16. Just during we submitted our manuscript and in the course of the manuscript was reviewed, Hideo Togo reported a new approach to aromatic ketones by oxidation of alkylarenes with Oxone-KBr-CH<sub>3</sub>NO<sub>2</sub> or Oxone-KBr-CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O: Moriyama, K.; Takemura, M.; Togo, H. Org. Lett. **2012**, 14, 2414. They used nitromethane (CH<sub>3</sub>NO<sub>2</sub>) as one of the main solvent, which is easy to explode.