In situ Formation of $NO_{\rm x}$ and Br Anion for Aerobic Oxidation of Benzylic Alcohols without Transition Metal

Guanyu Yang,*a Wei Wang, Weimin Zhu, Cunbin An, Xinqin Gao, Maoping Song*a

^a Department of Chemistry, Zhengzhou University, 75 Daxue Road, Zhengzhou 450052, P. R. of China Fax +86(371)67763927; E-mail: yangguanyu@zzu.edu.cn; E-mail: mpsong9350@zzu.edu.cn

^b State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116012, P. R. of China

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Abstract: The reaction of KBrO₃ and NH₂OH·HCl in situ generates NO_x and Br anion, which combine with 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) to construct a NO-activating dioxygen, Brassisted, TEMPO-catalyzed aerobic oxidation of alcohols. Catalyzed by KBrO/NH₂OH·HCl/TEMPO, various benzylic alcohols can be oxidized quantitatively to their corresponding carbonyl compounds under mild conditions. The easy handling and simple product separation make the process an attractive candidate for the oxidation of alcohols.

Key words: oxidation, alcohols, catalyst, bromate, hydroxylammonium, 2,2,6,6-tetramethylpiperidine-*N*-oxide

The oxidation of alcohols to the corresponding aldehydes and/or ketones is of fundamental importance in synthetic research and industrial manufacturing.1 Use of molecular oxygen as the terminal oxidant is of economic and environmental benefits in the oxidation of organic compounds. Various investigations showed that 2,2,6,6tetramethylpiperidine-N-oxide (TEMPO), as a small molecule organocatalyst, could efficiently and selectively catalyze the aerobic oxidation of alcohols in combination with some transition-metal cocatalyst² such as Cu-Mn mixed oxide,³ NaNO₂/FeCl₃,⁴ Mn(NO₃)₂/Co(NO₃)₂ or $Mn(NO_3)_2/Cu(NO_3)_2$,⁵ Cu complexes,⁶ and RuCl₂(PPh₃)₃.⁷ Recently, an interesting transition-metal-free catalytic system encompassing Br₂, NaNO₂, and TEMPO was reported for the aerobic oxidation of alcohols.⁸ The catalytic mechanism involves three tandem reaction cycles: 1) a redox cycle of NO and NO₂ responsible for activating the molecular oxygen, 2) a redox cycle of TEMPO and its oxoammonium cation resulting in the oxidation of alcohols to the corresponding carbonyl compounds, and 3) the redox cycle of Br₂ and HBr bridging between the above two cycles. This system was further improved by using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as a bromine source instead of Br₂,⁹ and *tert*-butyl nitrite (TBN) as an efficient NO equivalent instead of NaNO2,¹⁰ respectively. Catalyzed by TEMPO/NaNO₂/Br₂, TEMPO/ NaNO₂/DBDMH, or TEMPO/TBN/HBr, a wide range of alcohols could be converted to their corresponding aldehydes or ketones in high yields. However, organic TBN and DBDMH are unstable, and the handling of them, as well as hazardous Br_2 , requires precaution procedures that are difficult to handle in industrial-scale applications.

It is known that the reaction of KBrO₃ and the nitrogencontaining compounds can produce nitrogen oxides, bromide anion, and oxybromo species.¹¹ This implies that the reaction of KBrO₃ and NH₂OH·HCl could occur as depicted in Equation 1.

So by using $KBrO_3$ and $NH_2OH \cdot HCl$ together in the TEMPO-catalyzed aerobic oxidation of alcohols, NO, NO₂, and Br anion could be generated in situ and then serve as cocatalysts. Herein, we report an aerobic alcohol oxidation under mild conditions, using $KBrO_3$, $NH_2OH \cdot HCl$, and TEMPO as catalytic system.

The aerobic oxidation of alcohols was performed using benzyl alcohol as the model substrate in dichloromethane under dioxygen (0.30 MPa) at room temperature (Table 1).¹² The initial test (entry 1) gave an encouraging result that a complete conversion of benzyl alcohol to benzaldehyde was realized by using 10 mol% of TEMPO, 10 mol% of NH₂OH·HCl, and 5 mol% of KBrO₃ as catalysts, and no noticeable overoxidation to benzoic acid was detected. And this clearly showed that the KBrO₃/ NH₂OH·HCl/TEMPO system exhibited good catalytic performance. In sharp contrast, the reaction occurred barely in the absence of any component of the catalyst under the same conditions (entries 2-4). In addition, using $KBrO_3$ alone gave the conversion of 1.9% (entry 5), meaning that benzyl alcohol was oxidized less effectively by KBrO₃. And it was noteworthy that when the atmosphere over the mixture was replaced with O_2 three times in the case of using the three catalytic components together, the conversion was only 2.6% (entry 6). The possible cause could be that the gaseous NO and NO₂, the real active components of the catalytic system, were missing during the atmosphere replacement, and, as a result, the oxidation did not work well. These preliminary results

 $4 \text{ KBrO}_3 + 6 \text{ NH}_2\text{OH} \cdot \text{HCI} \longrightarrow 3 \text{ NO} + 3 \text{ NO}_2 + 4 \text{ Br}^- + 6 \text{ CI}^- + 6 \text{ H}^+ + 4 \text{ K}^+ + 9 \text{ H}_2\text{O}$

Equation 1

SYNLETT 2010, No. 3, pp 0437–0440 Advanced online publication: 15.01.2010 DOI: 10.1055/s-0029-1219202; Art ID: W16609ST © Georg Thieme Verlag Stuttgart · New York suggested that the reaction of $KBrO_3$ and NH_2OH ·HCl could occur easily to in situ generate NO, NO₂, and Br anion, as expected, and all of them with TEMPO constructed the tandem triple catalytic cycles, which promoted the aerobic oxidation.

Further investigations on this novel three-component catalytic system for the benzyl alcohol oxidation are shown in Table 1. As can be seen, the decrease in the loading amounts of each component led to the rate decrease of oxidation to different degrees, but the low dosage of TEM-PO still had a significant catalytic activity. Decreasing the load amount of TEMPO to 0.1 mol% in the presence of 10 mol% NH₂OH·HCl and 5 mol% KBrO₃, oxidation proceeded in only 34.5% conversion in the course of 3 hours (entry 12), although benzyl alcohol was completely oxidized to benzaldehyde (entry 13) by prolonging the time to 24 hours under the same conditions.

The conversion reached as high as 98.3% under the same conditions in the presence of 0.5 mol% of TEMPO (entry 10). Hence, 0.5 mol% was chosen as the loading amount of TEMPO in the further optimization tests. It was obvious that the loading amount of NH₂OH·HCl and KBrO₃ had a greater influence on the rate than that of TEMPO; 58.9% product conversion was realized in the presence of 0.5 mol% TEMPO, 5 mol% NH₂OH·HCl, and 5 mol% $KBrO_3$ (entry 14), but a lower conversion (20.4%) was obtained in the presence of 3 mol% KBrO₃ and 10 mol% NH₂OH·HCl (entry 18). Further decreasing the loading amounts of both NH₂OH·HCl and KBrO₃ to 0.5 mol% failed to give good yields of the oxidation product (entries 17 and 20). As documented before, $^{8-10}$ a cascade of redox tricycle reactions is involved in such transition-metal-free oxidation systems. We suggested that the TEMPO redox should proceed faster than the redoxes of NO_x and Br anion, and therefore, the loading amounts of NH₂OH·HCl and KBrO₃ should be more than the amount of TEMPO in order to keep the three reaction cycles proceeding.

The system was employed further in catalyzing the aerobic oxidation for various alcohols. The oxidations of all alcohols were analyzed by GC-MS analysis, and, to our expectation, the corresponding carbonyl compounds were the sole organic products. Each oxidation test was determined with GC measurement. If the oxidation of the alcohol substrate was not completed, the reaction was repeated again by prolonging the reaction time until no alcohol could be detected by GC analysis. Due to the watersolubility of TEMPO and other inorganic residues, isolations of the corresponding carbonyl compounds were performed easily by merely washing the reaction mixture with water several times. The isolated carbonyl compounds were characterized by ¹H NMR spectroscopy (see Supporting Information). The isolated yields and some GC yields were presented in Table 2.¹³ As can be seen, by increasing the temperature from room temperature to 50 °C with the optimized amounts of the catalysts (0.5 mol% of TEMPO, 10 mol% of NH₂OH·HCl, and 5 mol% of KBrO₃), oxidation of benzyl alcohol was accomplished in the shorter course of two hours. Similar temperature ef-

Entry	TEMPO (mol%)	NH ₂ OH·HCl mol(%)	KBrO ₃ (mol%)	Conv. (%) ^b
1	10	10	5	100
2	0	10	5	1.2
3	10	0	5	0.5
4	10	10	0	0
5	0	0	5	1.9
6 ^c	10	10	5	2.6
7	5	10	5	100
8	3	10	5	100
9	1	10	5	100
10	0.5	10	5	98.3
11	0.3	10	5	63.8
12	0.1	10	5	34.5
13 ^d	0.1	10	5	100
14	0.5	5	5	58.9
15	0.5	3	5	33.8
16	0.5	1	5	20.7
17	0.5	0.5	5	1.5
18	0.5	10	3	20.4
19	0.5	10	1	33.4
20	0.5	10	0.5	6.3

^a The oxidations were carried out using 2 mL benzyl alcohol (19.33 mmol) and 10 mL CH_2Cl_2 under ≤ 0.3 MPa O_2 for 3 h in all cases. ^b The conversions and the selectivities were based on GC with area normalization; the selectivities of benzaldehyde were 100% in all case.

 $^{\rm c}$ The atmosphere over the mixture was replaced with O_2 for three times before stirring began.

^d For 24 h.

fect was observed in the oxidations of *p*-methylbenzyl alcohol, *p*-methoxybenzyl alcohol, and *p*-chlorobenzyl alcohol. For *p*-nitrobenzyl alcohol, due to the presence of an electron-withdrawing nitro group, the oxidation needed 24 hours to realize 97.5% conversion at 50 °C. However, with a higher TEMPO loading (1 mol%) at a higher temperature (80 °C), the complete oxidation could also be achieved in a shorter time of six hours. Furthermore, no matter where the methyl is located, all methylbenzyl alcohols could be oxidized to the corresponding aldehydes under the same conditions. On the other hand, cinnamyl alcohol, 2-phenethanol, and cyclohexanol were oxidized in isolated yields of 95%, 93%, and 77%, respectively, under slightly different reaction conditions.

Alcohol	TEMPO (mol%)	Temp (°C)	Time (h)	Products	Yield (%) ^b
OH OH	0.5	50	2	Сно	97°
OH OH	0.5	25	8		95.9
	0.5	80	6	— СНО	96 ^c
∕=_\Он	0.5	25	12		85.7
MeO-	0.5	50	12	MeO	99°
,OH	0.5	25	24		89.6
CI	0.5	50	12	СІ—	93°
OH OH	0.5	50	24		97.5
0 ₂ N-	1.0	80	6	O ₂ N-CHO	97°
ОН	0.5	80	6	СНО	93°
ОН	0.5	80	6	Сно	98°
ОН	0.5 1.0	25 80	18 12	СНО	40.5 95°
ОН	0.5 1	25 80	24 6		98.2 93°
он	0.5 5	25 25	24 24	 o	64.0 77°

 Table 2
 Oxidation of Different Alcohols Catalyzed by KBrO₃/NH₂OH·HCl/TEMPO^a

^a The reactions were carried out under 0.3 MPa of dioxygen in 10 mL of CH_2Cl_2 ; the used amounts of solid substrates were 1.0 g and liquid were 2 mL; 5.0 mol% of KBrO₃ and 10.0 mol% of NH₂OH·HCl were used in all case.

^b GC yields.

^c Isolated yields.

In summary, a transition-metal-free, efficient catalytic system consisting of KBrO₃, NH₂OH·HCl, and TEMPO was developed that was able to perform the aerobic oxidations of various alcohols to their corresponding carbonyl compounds under mild conditions. During the catalytic process, the reaction of KBrO₃ and NH₂OH·HCl could in situ generate NO_x and Br anion. The redox cycle of NO_x played an important role in activating molecular oxygen for this Br-assisted, TEMPO-catalyzed aerobic oxidation. The easy handling and simple separation make the process an attractive method for the oxidation of alcohols.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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- (12) General Typical Procedure for the Oxidation The reaction was carried out in a 70 mL autoclave, and the general procedure is described typically with benzyl alcohol as follows: To a reactor were added benzyl alcohol (2 mL, 19.3 mmol), NH₂OH·HCl (174.8 mg, 10 mol%), KBrO₃ (161.2 mg, 5 mol%), TEMPO (15.1 mg, 0.5 mol%), and CH₂Cl₂ (10 mL). The closed autoclave was charged with O₂ to 0.3 MPa and warmed to 80 °C under stirring. The pressure of O₂ was kept under 0.4 MPa for 2 h. After cooled to r.t., 20 mL CH₂Cl₂ were added to the autoclave. Then the solution was analyzed by gas chromatography, which was conducted using an Agilent Technologies 6890N Network GC System with a flame ionization detector and a DB-1 capillary column (30 m × 0.535 mm × 3.0 µm).
- (13) General Isolation Procedure for the Oxidation Product After GC showed the reaction to be complete, the reaction mixture was diluted with CH₂Cl₂ and transferred into a separation funnel. The CH₂Cl₂ solution was washed with 15 mL of a sat. solution of Na₂CO₃, followed by brine. The organic layer was dried over anhyd Na₂SO₄, and the solvent was evaporated to yield the product without further purification.

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