

TEMPO-catalyzed oxidation of benzylic alcohols to aldehydes with the H₂O₂/HBr/ionic liquid [bmim]PF₆ system

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Abstract—A selective oxidation of benzylic alcohols to the corresponding aldehydes in room temperature ionic liquid was achieved by using TEMPO/HBr/H₂O₂ system, and both ether-insoluble acetamido-TEMPO and ionic liquid [bmim]PF₆ can be successfully recovered and reused for the oxidation of the same (different) substrate.

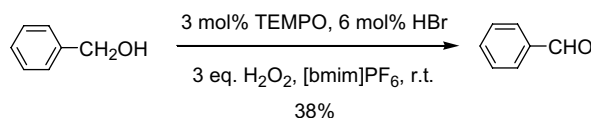
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The oxidation of alcohols into the corresponding aldehydes or ketones is a fundamental reaction in both laboratory and industrial synthetic chemistry.¹ Usually, environmentally hazardous oxidizing agents (i.e., KMnO₄, MnO₂, CrO₃, SeO₂, etc.) in stoichiometric amount are necessary to perform this transformation.² With the increasingly environmental consciousness of academia and industry research, the search for more effective catalytic oxidation process that use clean, inexpensive terminal oxidants, such as molecular oxygen or aqueous hydrogen peroxide, remains an important challenge.³ Recently, many examples of homogeneous systems making use of palladium,⁴ ruthenium,⁵ copper,⁶ or cobalt⁷ compounds as catalysts for aerobic alcohol oxidation with molecular oxygen as terminal oxidant have been reported. However, most of these catalytic systems are performed in aromatic or halogenated hydrocarbon solvents with low catalytic activity.

On the other hand, the reduction/replacement of volatile organic solvents from the reaction media is of high priority in the Green Chemistry focus area.⁸ Ionic liquids, composed entirely of ions with melting point below 100 °C,⁹ are now emerging as promising and attractive alternatives due to their unique properties including low volatility, high polarity, stability over a wide temperature range, and capacity to dissolve a variety of organic, inorganic, and organometallic compounds.

Furthermore, a proper choice of cation and anion provides a fine-tuning of their miscibility with water and common organic solvents. Thus, ionic liquids have been used as solvents in a wide range of organic reactions, such as Diels–Alder,¹⁰ Friedel–Crafts,¹¹ Heck,¹² and Suzuki¹³ coupling reactions, hydroformylation,¹⁴ hydrogenation,¹⁵ olefin dimerization,¹⁶ and oligomerization.¹⁷ However, only recently have the potential benefits of oxidation in ionic liquids been examined. Reported reactions include Ni(acac)₂-catalyzed aerobic oxidation of aromatic aldehydes,¹⁸ ruthenium-catalyzed,¹⁹ or copper-TEMPO-catalyzed²⁰ aerobic oxidation of alcohols, palladium-catalyzed oxidation of styrene²¹ and benzyl alcohol,²² osmium-catalyzed dihydroxylation of alkenes,²³ and rhenium-catalyzed Baeyer–villiger reaction.²⁴

Our interest in exploring the potential of aqueous hydrogen peroxide as green oxidant prompted us to investigate alcohol oxidation in ionic liquids. Inspired by the results of TEMPO–Br₂/I₂ system for alcohol oxidation²⁵ and H₂O₂–HBr system for benzylic bromination,²⁶ we now report a highly selective oxidation of benzylic alcohols to aldehydes using a three-component catalytic system consisting of H₂O₂, HBr, and TEMPO with an ionic liquid as the solvent.



Scheme 1.

Keywords: TEMPO; Alcohol oxidation; Benzylic alcohols; Ionic liquids; [bmim]PF₆.

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Table 1. Optimization of the reaction conditions for oxidizing benzyl alcohol to benzaldehyde^a

Entry	H ₂ O ₂ /PhCHO ratio	Conv./Sel. (%) ^b	Yield (%) ^c
1	3	98/99	90
2 ^d	3	36/97	31
3 ^e	3	38/99	36
4 ^f	3	6/99	—
5	2	98/97	89
6 ^g	2	98/98	92
7 ^h	2	98/98	90
8 ^h	2	99/96	92
9 ^h	2	99/97	88
10 ^h	2	98/96	91

^a 2 mmol benzyl alcohol, 50% aqueous H₂O₂, 3 mol % TEMPO, 6 mol % HBr, 1 mL [bmim]PF₆, 40 °C, 2 h.

^b Conversion and selectivity were determined by ¹H NMR of the crude product mixture.

^c Isolated yield by flash chromatography.

^d 1 mL EtOAc as solvent.

^e 1 mL CHCl₃ as solvent.

^f 3 mol % I₂ was used to replace HBr.

^g Acetamido-TEMPO was used as catalyst.

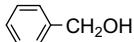
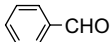
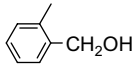
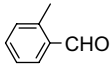
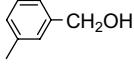
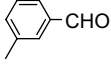
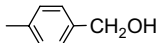
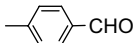
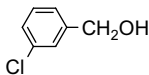
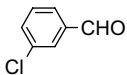
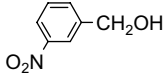
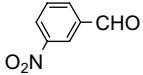
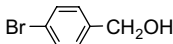
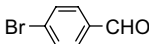
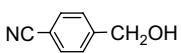
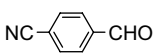
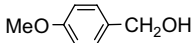
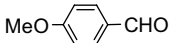
^h Recycling experiment for both [bmim]PF₆ and catalyst acetamido-TEMPO.

The room temperature ionic liquid [bmim]PF₆ was chosen, due to its immiscibility with water, and the initial

study was carried out using benzyl alcohol as substrate and 3 equiv of aqueous hydrogen peroxide (50%) at ambient temperature in the presence of 6 mol % HBr and 3 mol % TEMPO (Scheme 1). The oxidation proceeded smoothly and 38% isolated yield of benzaldehyde was obtained with 42% conversion and 98% selectivity (2% benzoic acid detected by ¹H NMR) after 2 h stirring. Increasing the reaction temperature to 40 °C, 98% conversion and 90% isolated yield was obtained under the identical condition.

Further efforts were then focused on optimizing the reaction condition. The conversion, selectivity, and yield of the oxidation under different conditions are summarized in Table 1. For the comparison, the common organic solvents, ethyl acetate, and chloroform, were also tested for the oxidation of benzyl alcohol under the same condition, and reasonable conversions and yields were obtained (Table 1, entries 2 and 3). At the same time, iodine (3 mol %) was used to replace aqueous HBr as co-catalyst for the oxidation, and only 6% conversion was detected by ¹H NMR of the crude reaction mixture. Recognizing that H₂O₂ was partially decomposed during the reaction, we sought to reduce the amount of hydrogen peroxide by adding it in two portions. Indeed, 98% conversion, 97% selectivity, and

Table 2. Oxidation of alcohols to aldehydes in [bmim]PF₆^a

Entry	Benzylic alcohols	Condition	Products	Yields (%) ^b
1		2 equiv H ₂ O ₂ , 2 h		92
2		2 equiv H ₂ O ₂ , 3 h		83
3		2 equiv H ₂ O ₂ , 3 h		81
4		2 equiv H ₂ O ₂ , 2 h		87
5		3 equiv H ₂ O ₂ , 4 h		93
6		5 equiv H ₂ O ₂ , 4 h		72 ^c
7		3 equiv H ₂ O ₂ , 4 h		91
8		4 equiv H ₂ O ₂ , 4 h		83
9		2 equiv H ₂ O ₂ , 2 h		—

^a The reactions were carried out in 2 mmol scale at 40 °C.

^b Isolated yield by flash chromatography.

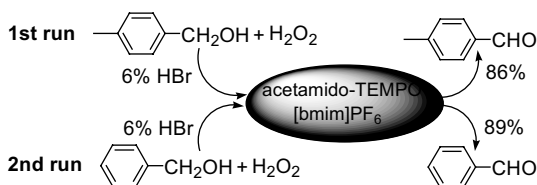
^c The reaction was carried out at 50 °C.

89% isolated yield was obtained even by using 2 equiv of hydrogen peroxide (Table 1, entry 5).

Furthermore, TEMPO is a rather expensive chemical agent, and efficient recycling of TEMPO is very desirable. Several groups have addressed this problem by designing and synthesizing heterogeneous variant of TEMPO.²⁷ In our present reaction condition, TEMPO cannot be reused in ionic liquid after ether extraction, due to its good solubility in ether. Surprisingly, we found that the commercial available acetamido-TEMPO has very good solubility in [bmim]PF₆, but is insoluble in ether, which encouraged us to recycle acetamido-TEMPO in [bmim]PF₆ for this oxidation. To our delight, acetamido-TEMPO afforded the comparable conversion, selectivity, and yield (Table 1, entry 6). A second run was then performed by adding fresh benzyl alcohol, hydrogen peroxide, and 6 mol % aqueous HBr to the ionic liquid under the same experimental conditions. It was noteworthy that the benzaldehyde was obtained in the similar conversion, selectivity, and yield without addition of acetamido-TEMPO, indicating that both the ionic liquid and the catalyst were recoverable and reusable (Table 1, entry 7). This catalytic system was stable and efficient for three more recycling without significant loss of catalytic capability (Table 1, entries 8–10). To the best of our knowledge, this is the first example to use an ionic liquid to retain a TEMPO derivative for efficient recycling.

Subsequently, the three-component catalytic system was then applied to various benzylic alcohols as summarized in Table 2.²⁸ Both electron-deficient and electron-neutral benzylic alcohols afforded good to excellent isolated yields. However, electron-rich benzylic alcohol, *p*-methoxybenzyl alcohol only gave a trace amount of aldehyde and 6% of the by-product *p*-methoxybenzyl bromide (determined by ¹H NMR of the crude reaction mixture), which consumed the co-catalyst HBr and ended the catalytic cycle.²⁹

In addition to recycling of the ionic liquid and acetamido-TEMPO for the same substrate, it is also important to verify the viability of reusing the catalytic system for different reactions, which was confirmed by two consecutive reactions (Scheme 2). After the oxidation of *p*-methylbenzyl alcohol to the aldehyde, the recovered [bmim]PF₆ and acetamido-TEMPO were reused for the oxidation of benzyl alcohol to benzaldehyde, and the ¹H NMR analysis of the crude mixture of the second reaction indicated no contamination of the earlier product (<1%).



Scheme 2.

In conclusion, an efficient oxidation of benzylic alcohols to aldehydes by using TEMPO/HBr/H₂O₂ system has been achieved in ionic liquid [bmim]PF₆. The electron-deficient and electron-neutral benzylic alcohols were oxidized in good to excellent yields, whereas the electron-rich benzylic alcohol failed to afford the target product due to side-reaction. The process is simple and mild. Most importantly, the ether-insoluble acetamido-TEMPO can be recycled and reused in ionic liquid [bmim]PF₆ for the oxidation of the same (different) substrate.

Acknowledgments

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28. A general procedures for the oxidation of benzylic alcohols follow: to a solution of benzyl alcohol (216 mg, 2 mmol), 50% aqueous hydrogen peroxide (272 mg, 4 mmol, in two portion) and acetamido-TEMPO (13.0 mg, 3 mol %) in 1 mL room temperature ionic liquid [bmim]PF₆ was added 48% aqueous hydrobromic acid (20 mg, 6 mol %). The reaction mixture was capped and stirred at 40 °C for 2 h, and the reaction mixture was extracted with ethyl ether (3 × 5 mL). The combined ether phase was washed with saturated brine (2 × 5 mL) and dried by anhydrous MgSO₄. Evaporation of ether gave a crude mixture for ¹H NMR analysis, and then was purified by flash chromatography (hexanes:ethyl ether = 10:1) to afford benzaldehyde (195 mg, 92%).
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