



Highly practical oxidation of benzylic alcohol in continuous-flow system with metal-free catalyst



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ABSTRACT

Oxidation of benzylic alcohol to ketone or aldehyde is one of the most challenging reactions in terms of green chemistry. We report herein that employing H₂O₂, catalytic amount of Br⁻ and acid in continuous-flow system to realize oxidation of benzylic alcohols with broad substrate scope and high selectivity. More importantly, no over oxidation to acid was obtained and it showed higher selectivity to 2° hydroxyl groups rather than 1°.

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As an important fundamental synthetic reaction, selective oxidation of benzylic alcohols to aldehydes and ketones is one of the most challenging reactions in green chemistry. A number of classical reagents have been developed, including chromium and manganese oxides,^{1–3} TEMPO,^{4,5} Swern reagents,^{6,7} and Dess–Martin reagents.^{8,9} However, either stoichiometric heavy metal complexes or hazardous operation is involved in these processes, which limits the reaction to small-scale. During past decades, intensive research has been focused on developing new catalyst systems, such as Pd^{10–12} and Ru.^{13–15} Various alcohols have been oxidized effectively with these catalysts. However, these catalysts can be inhibited by heterocycles and other nitrogen-, oxygen-, and sulfur-containing functional groups.¹⁶ It was possibly because that the noble metal catalyst was inhibited and inactivation by forming the coordinate bond between heteroatoms and metals. Meanwhile, high cost is another significant limitation in terms of large-scale applications. Consequently, selective oxidation of benzylic alcohols with mild, green, and economic process is still a big challenge in organic synthetic chemistry.

In 1920, bromine had been employed as an oxidant for selective oxidation of alcohols and phenols.^{17–19} Unfortunately, the method

was faded away, since bromine was a toxic, dangerous, and environmentally harmful reagent. In recent years, several oxidation systems with the assistance of bromide have been developed.^{20,21} However, either complicated catalyst or environmental unfriendly solvent was involved in these processes. Meanwhile, these developed oxidation systems showed less reactivity to starting materials of electron-deficient benzylic alcohols.

In this study, a novel selective oxidation of benzylic alcohols to aldehydes and ketones was established by using stoichiometric H₂O₂ (30% aq) together with the catalytic amount of Br⁻ and acid without any metal catalyst. Generally, this new-built methodology addressed a more efficient, economic, environmental friendly oxidation protocol compared with typical processes. Although bromide played a significant role in the reaction pathway, it was not consumed throughout the oxidation process.

In the model reaction, 4-nitrobenzyl alcohol was chosen to optimize the Br⁻ source because of its relatively low reactivity in traditional oxidation process. The results are summarized in Table 1.

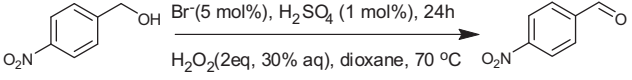
According to results in Table 1, bromine systems yielded much better results (~70%, Table 1, entries 1–5) than iodine systems and chlorine systems. More importantly, over oxidation of hydroxyl group to acid was observed in iodine systems, which reduced the selectivity of the oxidation dramatically. The corresponding acid was isolated at yields of ~20% in iodine systems (Table 1, entries 6 and 7). Effects of chlorine systems could be ignored compared

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Table 1
Optimization of $\text{H}_2\text{O}_2/\text{Br}^-/\text{H}^+$ oxidation system for the oxidation of 4-nitrobenzyl alcohol



Entry	Bromine sources ^a	Yield ^b (%)
1	NaBr	72
2	KBr	72
3	NBS	74
4	TBAB	68
5	CTMAB	67
6 ^d	KI	21 (19 ^c)
7 ^d	TBAI	25 (22 ^c)
8 ^d	TEAC	6
9 ^d	TEBAC	5
10	-	5

^a NBS: *N*-bromosuccinimide, TBAB: tetrabutyl ammonium bromide, CTMAB: hexadecyltrimethyl ammonium bromide, TEAC: tetraethyl ammonium chloride, TEBAC: benzyltriethyl ammonium chloride.

^b Yield of isolated product.

^c Yield of isolated over oxidation product of acid.

^d I^- and Cl^- were employed.

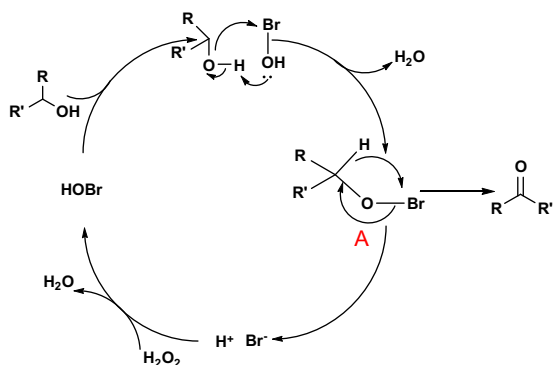


Figure 1. Proposed mechanism of the oxidation.

with reaction without any catalyst (Table 1, entries 8–10). Interestingly, there was no big difference obtained with NaBr, KBr, NBS, TBAB, and CTMAB as bromine sources. NaBr was employed in further reactions because it was economic and commercial available.

A possible mechanism was proposed as shown in Figure 1.¹⁸ Initially, Br^- was oxidized to form the hypobromous acid in the presence of acid and hydrogen peroxide. The generated hypobromous acid subsequently reacted with the corresponding hydroxyl group to form the hypobromite intermediate A, which yielded the corresponding carbonyl compounds via α -hydrogen elimination. Brønsted acid and Br^- were reformatted to maintain the system circularly. To confirm this proposed mechanism, hydrobromic acid (40%, aq), which was an important intermediate in the reaction pathway, was employed directly to replace Br^- source and sulfuric acid. A yield of 43% of aldehyde was isolated in the model reaction, which supported the mechanism strongly. However, bromination of aromatic ring was also observed in this hydrobromic acid protocol. The bromination phenomenon was also observed in $\text{H}_2\text{O}_2/\text{Br}^-/\text{H}^+$ system with over 1 mol % of acid used.

In further study, a variety of alcohols, both aromatic and aliphatic substrates were employed (Table 2). Oxidation of aromatic alcohols without sensitive substitution (Table 2, entries 1–4, 'Batch' column) was realized in yields of 72–94% while, there was no designed product obtained in oxidation of benzylic alcohols with sensitive functionalities (Table 2, entries 5 and 6, 'Batch' column).

Table 2
The oxidation of benzylic alcohols with $\text{H}_2\text{O}_2/\text{NaBr}$ in the coil reactor and batch systems

Entry	Alcohols	Products	Yield ^c (%)	
			Conti-flow ^a	Batch ^b
1			32	72
2			96	85
3			95	92
4			97	94
5			97	NA
6			88	NA
7			NA	NA
8			NA	NA

^a Reaction conditions in batch: dioxane (3 ml), alcohol (1 mmol), Br^- (5 mol %), sulfuric acid (1 mol %), hydrogen peroxide (2 mmol), 70 °C, 24 h.

^b Reaction conditions in continuous-flow system: store solution A: 0.667 M of alcohol in the dioxane, flow rate 0.327 ml/min; store solution B: 1.667 M of hydrogen peroxide, 5 mol % of sodium bromide, and 1 mol % of sulfuric acid in dioxane, flow rate 0.327 ml/min, 70 °C, 1.2 min.

^c Yield of isolated product.

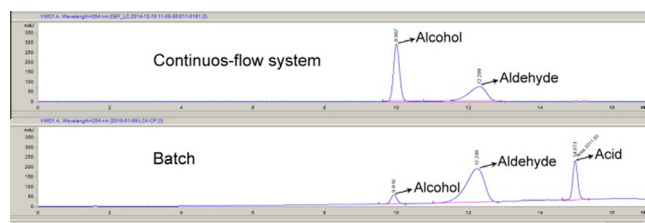


Figure 2. HPLC trace of reaction mixtures of oxidation of 4-nitrobenzyl alcohol.

This is probably because of the reactivity between amines/alkoxys and hypobromite restrained the oxidation. There was no oxidation of aliphatic alcohols (Table 2, entries 7 and 8, 'Batch' column) observed in the reaction, which is probably due to the low reactivity of aliphatic alcohols. To overcome these problems in the oxidation process, continuous-flow technique with benefits of high surface-to-volume ratio, efficient mass transfer and heat transfer, and high selectivity was employed in this study.^{22,23}

With an assembled continuous-flow system, all the reactions displayed in Table 2 were re-performed. Compared with batch condition, better reactivity, and selectivity of benzylic alcohols

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