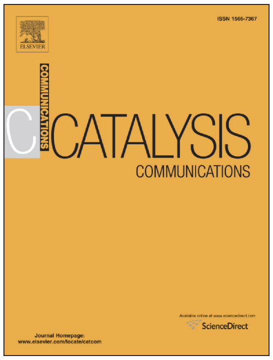

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Nitrogen dioxide-catalyzed aerobic oxidation of benzyl alcohols under cocatalyst and acid-free conditions

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ABSTRACT

Nitrogen dioxide is usually considered as a mediator between dioxygen and the catalysts for the aerobic oxidation of alcohols. Here, we report that nitrogen dioxide has an ability to catalyze this reaction, which not only avoids the use of the cocatalysts or the acids in traditional approaches, but also reveals a method for the present transformation with a single component catalyst. A series of primary and secondary benzyl alcohols underwent this transformation to give the targeted products in low to high yields.

Keywords:

Oxidation

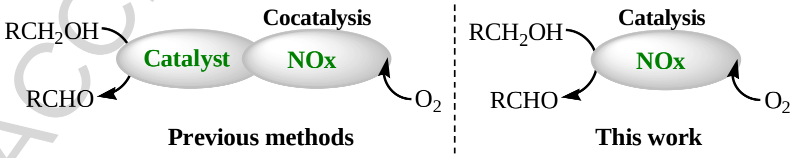
Benzyl alcohols

Nitrogen dioxide

Oxygen

1. Introduction

The selective oxidation of alcohols to aldehydes or ketones is considered to be an important and fundamental transformation in modern organic synthesis because the resulting products not only serve as the indispensable intermediates for the synthesis of many important fine chemicals, pharmaceuticals and agrochemicals, but also are the structural motifs frequently occurring in numerous drugs, vitamins and fragrances [1]. As a result, considerable efforts have been made to develop effective methods [2,3] for this transformation by using various oxidants, e.g. chromium-based reagents, permanganate, hypervalent iodine compounds, ruthenium tetroxide (RuO_4) and nitrogen dioxide [4]. Compared with other oxidants, the inexpensive and green oxygen is a more attractive alternative from both economic and green chemistry viewpoints [5-8]. However, the molecular oxygen is less reactive towards most organic molecules because it exists in the inactive triplet ground state. Thus an efficient activation of the molecular oxygen is usually crucial for its successful utility in the catalytic aerobic oxidation [9-14].



Scheme 1. The aerobic oxidation of alcohols in the presence of NOx.

Recently, NOx has attracted considerable attention as an effective cocatalyst to activate molecular oxygen in the aerobic oxidation of alcohols (Scheme 1). One example is the 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/HCl/$NaNO_2$ catalyst system [15,16], in which TEMPO plays a role of the catalyst, and the in situ generated

NO from HCl and $NaNO_2$ serves as a mediator between dioxygen and the catalyst. Other representative catalyst systems include AZADO/$NaNO_2$ [17], DDQ/AcOH/$NaNO_2$ [18], (TEMPO)/Br_2/$NaNO_2$ [19], 1-Me-AZADO/HNO_3/$NaNO_2$ [20], nanoshell carbon/HNO_3 [21], HNO_3/$NaNO_2$/amberlyst-15 [22,23], HBr/$NaNO_2$ [24], 5-F-AZADO/AcOH/$NaNO_2$ [25]. By all appearance, it should be desirable to simplify these sophisticated multi-component catalyst systems from environmental and economic perspectives. So we had attempted to develop a single component catalyst for the aerobic oxidation, and it was found that NO_2 had an ability to catalyze the aerobic oxidation of alcohols under cocatalyst and acid-free conditions, which provided an effective and practical method for the synthesis of arylaldehydes and arylketones.

2. Experimental

2.1. Materials and instruments

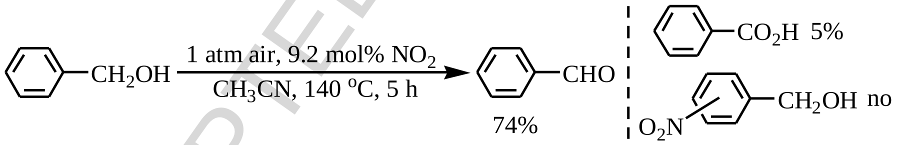
Commercially available compounds were purchased and used without purification unless otherwise stated, and the quality and suppliers of the chemicals are listed in Table S1 in the supporting information. Benzhydrol was synthesized by the reaction between the benzophenone and $LiAlH_4$.

GC-MS spectra was recorded on an Agilent 6890/5973N gas chromatography-mass spectrometry instrument. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 500 MHz instrument with chemical shifts reported in ppm relative to the internal standard tetramethylsilane. Gas chromatography analyses were performed on a Varian CP-3800 instrument with a FID detector and a CP-WAX 57CB FS capillary chromatographic column (25 m × 0.32 mm).

2.2. General procedure for the aerobic oxidation of various substrates

To a dried 45 mL tube equipped with a magnetic stirring, 2 mL acetonitrile, 0.5 mmol substrate and 0.046 mmol NO_2 were sequentially added (note: the air in the tube was not removed). Then the reaction tube was sealed and stirred magnetically at a constant-temperature to perform the reaction for 5 h. Once the reaction time was reached, GC analysis of the mixture provided the GC yields of the products. Then the crude product from another parallel experiment was purified by silica gel chromatography to give the desired product.

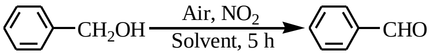
3. Results and discussion



Scheme 2. The selective oxidation of benzyl alcohol.

Our investigation began with the aerobic oxidation of benzyl alcohol under the condition that 0.5 mmol benzyl alcohol was stirred with 9.2 mol% nitrogen dioxide in 2 mL acetonitrile at 140 ^{o}C. As shown in Scheme 2, the reaction proceeded efficiently to give the benzaldehyde product in 74% yield, along with a small amount of benzoic acid by-product resulting from further oxidation of the targeted product. Although nitrogen dioxide had been reported to have an ability to nitrify the benzene ring [26-28], no nitration product was observed under the present condition. It was rational to assume that the residual oxygen in the reaction tube served as the oxidizing reagent. Indeed, the removal of oxygen from the reaction system resulted in a remarkable decrease in the product yield (Table 1, entry 3 vs entry 18).

Table 1. Aerobic oxidation of benzyl alcohol catalyzed by nitrogen dioxide.[a]



Entry	Loading of NO_2 (mol%)	Solvent	Temperature (°C)	Yield[b] (%)
1	-	acetonitrile	140	trace
2	4.6	acetonitrile	140	40
3[c]	**9.2**	**acetonitrile**	**140**	**74**
4[c]	13.8	acetonitrile	140	67
5[c]	13.8	acetonitrile	120	72
6	9.2	acetonitrile	40	8
7	9.2	acetonitrile	60	18
8	9.2	acetonitrile	80	34
9	9.2	acetonitrile	100	36
10	9.2	acetonitrile	120	65
11[c]	9.2	acetonitrile	160	70
12	9.2	THF	140	10
13	9.2	toluene	140	15
14	9.2	H_2O	140	5
15	9.2	DMF	140	43
16	9.2	CH_2Cl_2	140	53
17[d]	9.2	CH_2Cl_2	140	50
18[e]	9.2	acetonitrile	140	21

[a] Reaction conditions: 0.5 mmol benzyl alcohol, NO_2, 2 mL solvent, 5 h, 1 atm air. [b] Determined by GC with chlorobenzene as an internal standard. [c] Yield of benzoic acid by-product was respectively 5% (entry 3), 16% (entry 4), 6% (entry 5) and 9% (entry 11), while only trace amount of benzoic acid was observed under other condition. [d] 10mg amberlyst-15 was added. [e] Ar atmosphere.

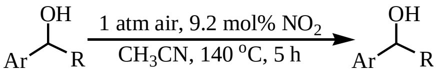
The reaction was highly dependent on the loading amount of NO_2. As shown in Table 1 (entry 1), the oxidation did not occur in the absence of NO_2, while an addition of 4.6 mol% NO_2 allowed reaction to give the targeted product in 40% yield (Table 1, entry 2). The yield of the targeted product greatly increased with increasing NO_2

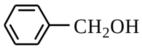
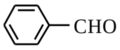
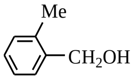
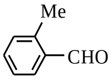
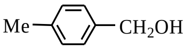
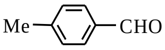
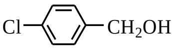
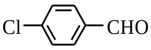
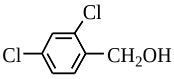
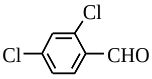
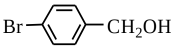
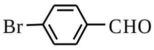
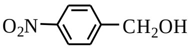
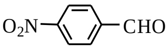
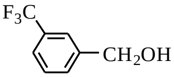
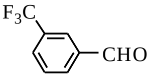
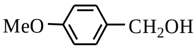
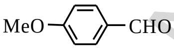
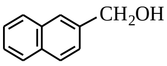
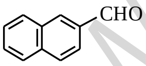
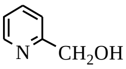
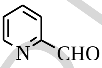
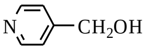
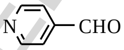
loading level up to 9.2 mol% but decreased as the loading level increased further (Table 1, entries 1-4), which suggested that 9.2 mol% was the optimal loading amount. It was also worth noting that an increase of the catalyst loading facilitated further oxidation of the targeted product to carboxylic acid. For example, when the loading amount of NO_2 was changed from 9.2 mol% to 13.8 mol%, the yield of benzoic acid as the overoxidation product increased from 5% to 16% (Table 1, entries 3 and 4).

Subsequently, we optimized other critical parameters such as temperature, solvent, additive, etc. The reaction temperature had a significantly effect on the results (Table 1, entries 3 and 6-11). The reaction at 40 ^{o}C gave a very low yield of 8%, while the reaction temperature of 120 ^{o}C allowed the desired product to be obtained in 65% yield. When 9.2 mol% catalyst was used, 140 ^{o}C was the optimal temperature in terms of the yield. An increase of the reaction temperature from 140 ^{o}C to 160 ^{o}C led to an increase in the yield of the benzoic acid by-product (Table 1, entry 3 vs entry 11). Among the screened solvents (Table 1, entries 3 and 12-16), acetonitrile turned out to be the most effective one, while the reactions using tetrahydrofuran, water or toluene were very sluggish. The presence of a Bronsted acid could often facilitate the oxynitride species-catalyzed aerobic oxidative reactions [26,29], which prompted us to add a Bronsted acid into the reaction system to improve the present reaction results. However, the presence of the Bronsted acid had almost no effect on the aerobic oxidation. For example, an addition of amberlyst-15 gave a similar yield with that in the absence of the acid (Table 1, entry 16 vs entry 17).

With the optimized results in hand, we set out to evaluate the scope of the present aerobic oxidation protocol. In most cases, the obtained isolated yields were significantly lower than those from gas chromatography or liquid chromatography under our conditions of separation and analysis, possibly due to the loss of the product in the course of the chromatographic purification. Generally, the present reactions were compatible with various groups, e.g. alkyl, chloro, bromo, nitro and trifluoromethyl groups (Table 2, entries 2-8). The benzyl alcohols with alkyl substituents were all good substrates (Table 2, entries 2 and 3). *ortho*-Methylbenzyl alcohol underwent this transformation in 70% GC yield, and similar result was obtained in the case of *para*-methylbenzyl alcohol, which revealed that the steric hindrance seemed to have a little influence on the reaction. When the benzyl alcohols with electron-withdrawing substituents were employed as the substrates, all the aerobic oxidation reactions proceeded smoothly with moderate to good GC yields (Table 2, entries 4-8). However, the reaction of the benzyl alcohol with a strong electron-rich substituent (methoxy group) gave the targeted product in a very low yield, and 71% substrate was recovered (Table 2, entry 9), which was rational to assume that the catalytic species was destroyed by the reaction between the electron-rich phenyl ring and NO_2 to prevent the oxidation from proceeding [26-28]. Indeed, 7% 4-methoxy-3-nitrobenzyl alcohol product from nitration of the substrate was observed in the case of 4-methoxybenzyl alcohol (Table 2, entry 9).

Table 2. Aerobic oxidation of various benzyl alcohols catalyzed by nitrogen dioxide. [a]



Entry	Substrate	Product[b]	GC yield[c] (%)	Isolated yield (%)
1			74	54
2			70	57
3			71	60
4			69	62
5			87	63
6			70	64
7			96	89
8			92	73
9[d]			16	–
10			72	56
11			93	–
12[e]			60	52
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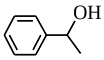
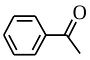
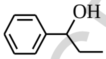
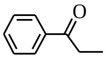
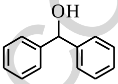
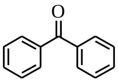
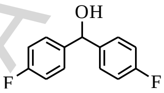
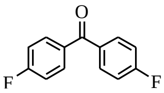
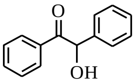
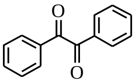
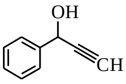
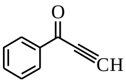
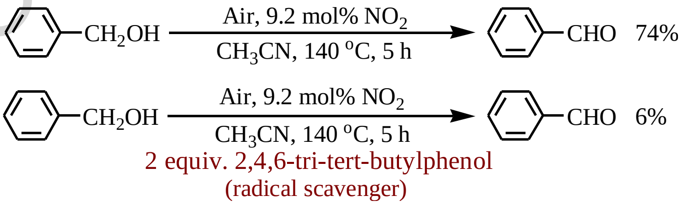
14			88	67
15			85	70
16			–	92
17			–	55
18			-	72
19			26	–

[a] Reaction conditions: 0.5 mmol substrate, 0.046 mmol (9.2 mol%) NO_2, 2 mL acetonitrile, 140 °C, 5 h, 1 atm air. [b] The product was characterized by ^{1}H-NMR, ^{13}C-NMR or mass spectra. [c] Determined by GC with chlorobenzene as an internal standard. [d] 7% 4-methoxy-3-nitrobenzyl alcohol and 71% substrate were observed after reaction. [e] 0.069 mmol NO_2, 120 °C.

Another kind of excellent substrates was naphthalenemethanols. For example, 2-naphthalenemethanol was selectively oxidized to the aldehyde product in 72% GC yield (Table 2, entry 10). 2-Pyridinemethanol underwent this transformation in 93% GC yield, while the reaction of 4-pyridinemethanol gave the targeted product in only 6% yield under the same condition (Table 2, entries 11 and 13). When 2-pyridinemethanol was used as the substrate (Table 2, entry 11), we had done our best to isolate the targeted product (determined by GC-MS), but it was puzzling that no purified product was obtained. The same phenomenon was also observed in the case using 4-methoxybenzyl alcohol or 1-phenyl-2-propyn-1-ol as the substrate (Table 2, entries 9 and 19), thus the isolated yields were not described in these cases.

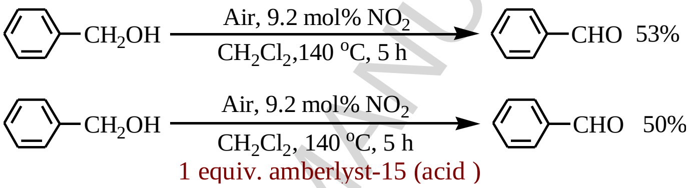
We found that the NO$_2$ catalyst could catalyze the oxidation of the secondary benzyl alcohols. Whether aryl alkyl alcohols or diaryl alcohols underwent this transformation to give the ketone products in moderate to high yields (Table 2, entries 14-17). Very interestingly, both 2-hydroxy-1,2-diphenylethanone and 1-phenyl-2-propyn-1-ol were smoothly oxidized to the ketone products (Table 2, entries 18 and 19).



Scheme 3. Effect of the radical scavenger on the reaction.

To gain insight into the reaction mechanism, we performed several control experiments where the well-known radical scavenger 2,4,6-tri-tert-butylphenol [22] was added into the reaction system. As shown in Scheme 3, the presence of

2,4,6-tri-tert-butylphenol led to a dramatic decrease in the yield of the aldehyde product. In addition, the addition of the Bronsted acid had almost no effect on the present reaction (Scheme 4), which is different from the ionic aerobic oxidation where the presence of a Bronsted acid can often facilitate the reaction [22,23,29]. These experimental results seem to be consistent with a free radical-based mechanism [23,30]. However, only based on these results, it can not be excluded that the present reaction undergoes an ionic pathway because that it is also possible that the presence of 2,4,6-tri-tert-butylphenol blocks the ionic reactions [30].



Scheme 4. Effect of the Bronsted acid on the reaction.

According to previous literatures [31], the reaction between nitrogen dioxide and alcohols can provide HNO_3 product that has an ability to catalyze aerobic oxidation of the benzyl alcohol [22], thus a HNO_3-catalyzed pathway is possible (for the detailed mechanism, see Ref. 22). Another possible mechanistic pathway involves an alpha-hydroxyl radical because that it is known that nitrogen dioxide [30] or the nitroxyl radical generated from NHPI (*N*-hydroxyphthalimide) [32] is prone to abstract hydrogen from an organic molecule to leave an alpha-hydroxyl radical. As shown in Scheme S1 (see the supporting information), the reaction starts with the reaction between benzyl alcohol and NO_2 [31]. The resulting radical can react with dioxygen to provide the aldehyde product based on previous literatures (Pathway A in

Scheme S1) [32,33]. It is also possible that the resulting radical is combinated with another molecule of NO_2 to give an α-hydroxynitrite intermediate [34], followed by the formation of the aldehyde product from a thermal decomposition of the nitrocarbinol (Pathway B in Scheme S1) [34,35].

4. Conclusions

In conclusion, nitrogen dioxide was found to have an ability to catalyze the aerobic oxidation of benzyl alcohols, which not only avoids the use of the cocatalysts or the acids in traditional approaches [15-25], but also reveals a strategy for the present transformation with a single component catalyst. The distinctive nitrogen dioxide catalyst can be easily separated from the final products, and is heavy metal waste-free. The present reactions were compatible with various groups, e.g. alkyl, chloro, bromo, nitro, trifluoromethyl and methoxy groups. A series of primary and secondary benzyl alcohols underwent this transformation to give the targeted products in low to high yields.

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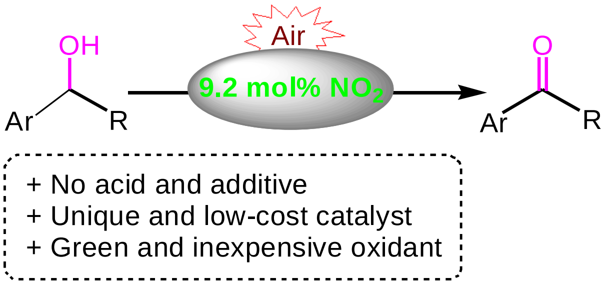
Graphical abstract



Nitrogen dioxide is usually considered as a mediator between dioxygen and the catalysts for the aerobic oxidation of alcohols. Here, we report that nitrogen dioxide has an ability to catalyze this reaction, which not only avoids the use of the cocatalysts or the acids in traditional approaches, but also reveals a method for the present transformation with a single component catalyst. A series of primary and secondary benzyl alcohols underwent this transformation to give the targeted products in low to high yields.

Research Highlights

► A practical method for selective oxidation of benzyl alcohols was developed. ► Nitrogen dioxide as a distinctive catalyst was used. ► The reactions proceeded smoothly under cocatalyst and acid-free conditions.