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tert-Butylnitrite as a convenient and easy-removable oxidant for the conversion of benzylic alcohols to ketones and aldehydes

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ABSTRACT

The oxidation of primary and secondary benzylic alcohols was achieved by using tert-butyl nitrite (t-BuONO) as a stoichiometric oxidant. Various substrates were effectively converted into the corresponding ketones or aldehydes in good to excellent yields. The reaction presumably proceeded by a nitrosyl exchange and a subsequent thermal decomposition of benzylic nitrites. This process would realize an oxidation of alcohols with oxygen in theory by combining with a reproduction of alkyl nitrites from NO and alcohols under an O_2 atmosphere. In addition, almost pure oxidized products were readily obtained by simple evaporation of the reaction mixtures since *t*-BuONO produced only volatile side products.

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Alkyl nitrites and sodium nitrite are frequently employed for several organic transformations including nitrosation and diazotization reactions.¹ In most cases, they act as a source of NO or nitrous acid in the reaction system. Although many reactions effectively progress by the solo use of alkyl nitrites, combinations with palladium or N-hydroxyphthalimide (NHPI) catalysts are employed for the production of industrially important materials such as dibutyloxalate² or nitrosocycloalkanes.³ Alkyl nitrites and sodium nitrite are also used for the oxidation of primary and secondary alcohols to corresponding aldehydes, ketones, and carboxylic acids with 2,2,6,6-tetramethylpiperidines (TEMPO) and/or halogenated compounds.⁴ These procedures are obviously more environmentfriendly than the classical methods using stoichiometric amounts of heavy metal based reagents. With the growing concern about green chemistry, developments of environmentally benign procedures are important issues. This time, we have found a novel feature of tert-butyl nitrite (t-BuONO) as a stoichiometric oxidant for benzylic alcohols. This procedure required neither metal based reagents nor organic catalysts. An evolution of NO gas during the reaction course might be a controversial matter, but several alkyl nitrites are industrially produced from the corresponding alcohols and gaseous NO under an O₂ atmosphere⁵ (Eq. 1). Ube Industries have translated a scheme of Pd/nitrites oxidation and reproduction of nitrites into practical applications to achieve a substantive oxygen oxidation process.^{2,5a} Thus, *t*-BuONO would realize an environmentally benign oxidation of alcohols by combining with the alkyl

* Corresponding author. E-mail address: mtok@chem.kyushu-univ.jp (M. Tokunaga). nitrite reproduction from the evolved NO. Additionally, since t-BuONO formed only volatile residual products, such as t-BuOH and gaseous NO, almost pure oxidized products were readily obtained by simple evaporation of the reaction mixtures. It was a meaningful advantage especially in the case of large scale reactions.

$$2 \text{ NO} + 2 \text{ ROH} + 0.5 \text{ O}_2 \rightarrow 2 \text{ RONO} + \text{H}_2\text{O}$$

$$\tag{1}$$

Table 1

Optimization of the reaction conditions for the oxidation of 1-phenylethanol^a



The reaction was conducted on 1 mmol scale in a sealed tube. ^b GC yield.



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Oxidation of 1-phenylethanol (**1a**) was examined under several conditions (Table 1). The various solvents could be used for the reaction, especially, toluene was found to be the most suitable of the tested solvents (Table 1, entries 1–6). The reaction efficiency was low in halogenated solvents (Table 1, entries 3 and 6), alluding to an involvement of a radical species. When the reaction was conducted without solvent, the amount of over-oxidized product **3a** was increased (Table 1, entry 7). A large excess of *t*-BuONO predictably gave a significant amount of **3a** (Table 1, entry 8).

With the optimal condition in hand, the substrate scope of the reaction was examined (Table 2). All 1-phenylethanol derivatives were smoothly oxidized to give the corresponding acetophenone derivatives in good to excellent yields (Table 2, entries 1–4). However, in the case of an electron rich substrate, the low selectivity was observed because of the over-oxidation (Table 2, entry 4). The substrates bearing a longer alkyl chain also gave good results (Table 2, entries 5 and 6). Diphenylmethanol was exclusively transformed into ketone product **2h** (Table 2, entry 7).

Next, we turned our attention to primary benzylic alcohols (Table 3). Under the optimal condition for the secondary alcohols, benzyl alcohol (**4a**) gave an almost 1:1 mixture of benzaldehyde (**5a**) and benzoic acid (**3a**) (Table 3, entry 1). The amount of **3a** was decreased under a diluted condition in 1 mL of toluene (Table 3, entry 2). Switching the solvent to DME and a lower reaction temperature of 100 °C dramatically improved the yield of **5a** (Table 3, entries 3 and 4). A more diluted condition did not show further improvement of the yield (Table 3, entry 5).

Table 2

Evaluation of the substrate in the oxidation of secondary benzylic alcohols^a



^a The reaction was conducted on 1 mmol scale in a sealed tube.

^b GC yield.

Table 3

Optimization of the reaction conditions for the oxidation of benzylalcohol^a



Entry	Solvent (mL)	Temp (°C)	Time (h)	Yield ^b (%)	
				5a	3a
1	Toluene (0.5)	120	10	30	37
2	Toluene (1)	120	8	34	15
3	DME (1)	120	6	50	7
4	DME (1)	100	17	89	7
5	DME (1.5)	100	18	58	7

^a The reaction was conducted on 1 mmol scale in a sealed tube.

^b GC yield.

The oxidation of various primary benzylic alcohols was examined (Table 4). All substrates gave corresponding aldehydes in good yields. The substrates bearing an electron withdrawing group exclusively afforded aldehydes **5** (Table 4, entries 2, 4, and 6). In the cases of electron rich substrates, over-oxidized products were obtained (Table 4, entries 1, 3, and 5). Heteroaromatic substrates were also suitable for the reaction (Table 4, entries 7 and 8).

To investigate the mechanism of the reaction, 1-phenylethanol (**1a**) and acetophenone (**2a**) were treated with gaseous NO (Scheme 1). The reaction started from **1a** gave a small amount of **2a** and **3a** through NO oxidation. On the other hand, oxidation of **2a** to **3a** smoothly proceeded with atmospheric NO in a 66% yield. These results suggested that **3a** was formed from **2a** and this over-oxidation step was assumed by NO, but not *t*-BuONO itself. The solvent effect on the over-oxidation observed in Table 1 may be explained by the solubility of NO in each solvent,⁶ but no specific relationship was found between them.

Next, acetophenone (**2a**) and dodecanophenone (**2g**) were treated with 3 equiv of *t*-BuONO (Scheme 2). The formation of **3a** suggested that gaseous NO was provided from *t*-BuONO. As an

Table 4

Evaluation of the substrate in the oxidation of primary benzylic alcohols^a

Ar \rightarrow OH $\xrightarrow{t-BuONO}$ (1.5 equiv.)Ar \rightarrow Ar \rightarrow CHO + Ar \rightarrow COOH \rightarrow 3

Entry	Substrate	Temp	Time	Aldehyde	Yiel	Yield ^b (%)	
		(°C)	(h)	product	5	3	
1	Ме	100	10	5b	74	26	
2	СІ	100	15	5c	74	Trace	
3	МеО	120	10	5d	71	28	
4	F ₃ C OH	100	12	5e	72	Trace	
5	<i>t</i> -Bu	120	8	5f	80	17	
6	O2N OH	120	10	5g	72	Trace	
7	€УОН	100	13	5h	82	17	
8	ОН	100	17	5i	71	Trace	

^a The reaction was conducted on 1 mmol scale in a sealed tube.

^b GC yield.



Scheme 1. Oxidation of 1-phenylethanol (**1a**) and acetophenone (**2a**) with gaseous NO.

additional evidence for the evolution of NO, a brown fume was observed when the sealed vessel was opened in air after the reaction. In the case of **2g**, a generation of undecanenitrile (**6**) was observed along with **3a**. This result indicated the C–C bond between carbonyl and the adjacent alkyl carbons was cleaved by the over-oxidation step.

On the basis of the above experimental results and the previous reports on the character of alkyl nitrites,^{7–10} the following mechanism was proposed (Scheme 3). A treatment of benzylic alcohol with *t*-BuONO resulted in a nitrosyl exchange.⁷ The formation of nitrosated intermediate was confirmed by an NMR experiment at 20 °C (Fig. 1). A thermal decomposition of alkyl nitrites takes place under heated conditions, but simple aliphatic nitrites generally requires a high temperature to attain sufficient reaction rates.⁸ According to Kornblum's report, 2-octyl nitrite needed 8 days for a complete decomposition at 100 °C.^{8b} On the other hand, benzyl nitrites sufficiently decompose even under a mild temperature below 100 °C.⁹ Therefore, the formation of a benzyloxy radical was in preference to that of a *t*-butoxy radical (Scheme 3, step 1). A subsequent



Scheme 2. Oxidation of acetophenone (2a) and dodecanophenone (2g) with *t*-BuONO.



Scheme 3. Plausible reaction mechanism for oxidation of benzylic alcohols with *t*-BuONO.



Figure 1. Observation of nitrosyl exchange between **1a** and *t*-BuONO in toluene-d₈. The spectra of **1a** in the presence of 3, 1.5, 1, 0.5, and 0 equiv of *t*-BuONO from top to bottom.

 α -hydrogen abstraction from another benzyl nitrite gave the carbonyl product, NO, and starting alcohol (Scheme 3, step 2). An over-oxidation of the product was attributed to NO from the reaction course and a partial decomposition of *t*-BuONO.¹⁰ The exact mechanism of over-oxidation was unclear, but the products and the participation of NO were reminiscent of a nitrosation of α -position¹¹ and subsequent Beckmann type fragmentation.¹² (Scheme 3, step 3).

According to the above reaction mechanism, at least 2 equiv of *t*-BuONO were necessary for the complete consumption of alcohols. Therefore, an involvement of other reaction paths should be considered since the reaction effectively proceeded with 1.5 equiv of *t*-BuONO. The thermal decomposition of nitrites generally gives an excess amount of oxidized products over alcohols,^{9b,9c} but not the equal amount presumed from Scheme 3, step 2. The inequality arose from a reduction of NO to HNO (Eq. 2 and 3), ^{9b,9c} and this reduction step likely participated in the reaction system. Another possibility including the formation of a methyl or phenyl radical from benzyloxy radicals^{8a,9b,9c} contradicted quantitative yields of the products. A direct rearrangement from benzyloxy radicals to a benzyl radical species was also experimentally negated.^{8b,9c}

$$\begin{array}{ll} \text{RCH}_2\text{O} &+ \text{NO} \rightarrow \text{RCH} = \text{O} + \text{HNO} & (2) \\ 2 & \text{HNO} \rightarrow \text{N}_2\text{O} + \text{H}_2\text{O} & (3) \end{array}$$

It was noteworthy that almost pure products were obtained by simple evaporation since *t*-BuONO left only volatile side products. In case of the oxidation of 1-phenylethanol, the crude residue after evaporation consisted of the compounds derived from the starting material. If necessary, a further purification could be readily performed by distillation.¹³ This was a great advantage especially in large scale synthesis.¹⁴

In conclusion, we have found a novel feature of *t*-BuONO to oxidize benzylic alcohols as a stoichiometric reagent. This method was environmentally benign since it did not require heavy metal based reagents or additional catalysts. Furthermore, almost pure products were obtained by a simple evaporation work-up, since *t*-BuONO produced only volatile side products such as *t*-BuOH and gaseous NO.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.006.

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- 13. Experimental procedure for oxidation of 1-phenylethanol (Table 1, entry 1): To a mixture of 1-phenylethanol (1a) (121μ L, 1 mmol), tridecane (50μ L, 0.205 mmol, internal standard) and toluene (0.5 mL) in a screw cap tube was added t-BuONO (Tokyo Chemical Industry Co., Ltd, >90%) (198 μ L, 1.5 mmol, 1.5 equiv) under N₂ atmosphere. The solution was stirred at 120 °C for 16 h. The reaction mixture was analyzed by GC and the product was isolated by column chromatography (SiO₂) for the characterization. The same procedure was applicable to 10 mmol scale reaction. The almost pure product was readily obtained by simple evaporation of the reaction mixture, and the further purification by vacuum distillation gave **2a** (968 mg, 81%) as a colorless oil.
- 14. Theoretically, the emission of NO could be completely avoided by the oxidative regeneration of nitrites as mentioned in the introduction part. However, a proper treatment for the evolved NO will be needed in the operation on a lab scale reactions.