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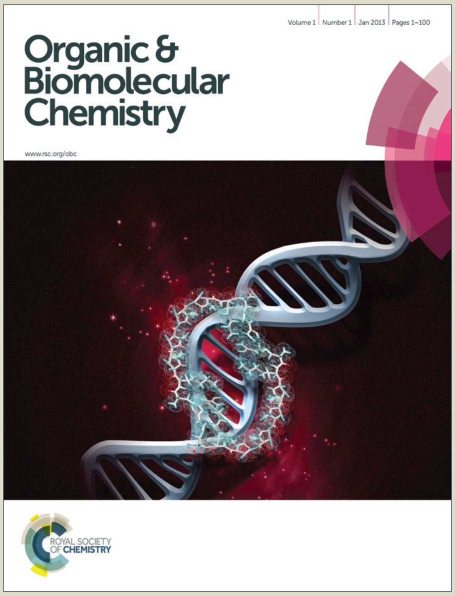

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ARTICLE TYPE

Oxidative cleavage of benzylic C-N bond under metal-free conditions

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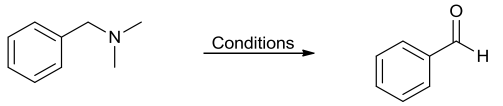
An interesting procedure for the oxidative cleavage of benzylic C-N bond has been developed. By using TBAI as the catalyst and H_2O_2 as the oxidant, various benzyl amines were transformed into the corresponding aromatic aldehydes in moderate to good yields. Notably, this is the first example on oxidative cleavage of benzylic C-N bond under metal-free conditions.

Benzylic amine is a class of prevalent functional group in organic chemistry, which has been used as ideal protecting group and substrates in organic synthesis.[1] Additionally, benzyl amines are present in natural products, pharmaceutical and bio-active molecules as well.[2] An effective and selective procedure for the cleavage of C-N bond offers more options to excess their derivatives and raising the potential to find alternative core structure with better bio-activities. On the other hand, aromatic aldehydes represent a high value class of compounds in organic chemistry, which could be widely used as an active formyl unit in the synthesis of other organic compounds, such as drugs, spices, dyes, pesticides and so on. Hence, a methodology based on benzyl amines to aldehydes is necessary and important.

Since the 20th century, provide 'Green' oxidation process has become a hot issue in new methodology development as the acceptance of 'sustainable development' by our community.[3] Thus, new reactions without the demand of expensive transition-metal catalysts have drawn more and more attention from organic chemists.[4] For example, the combination of tetrabutylammonium iodide (TBAI) and *tert*-butyl hydroperoxide (TBHP) is of great interest in oxidative transformation due to its inexpensive, high efficiency and benign environmental impact.[5] We have been interested in developing cheap and green oxidation procedures during last two years.[6] Oxidative procedures based on cheap metal catalysts or without metal catalyst have been developed. Here, we wish to report our recent results on the transition metal-free oxidative transformation of *N*,*N*-dimethylbenzyl amines to the corresponding aromatic aldehydes. By using TBAI as the catalyst and H_2O_2 as the green oxidant, benzyl amines were selectively and effectively transformed into the corresponding aldehydes in moderate to good yields.

Initially, we conducted the reaction by heating a solution of *N*,*N*-dimethylbenzyl amine **1a** in DMAc using 10 mol% TBAI and 2 equiv of TBHP. Gratifyingly, we got benzaldehyde **2a** in 45% yield (Table 1, entry 1). Encouraged by this result, we employed *N*,*N*-dimethylbenzyl amine **1a** as the model substrate to optimize the reaction conditions (Table 1). Subsequently, we examined the amount of TBHP, 4 equiv of TBHP gave better yield of aldehyde (Table 1, entry 2). It was noted that the yield of product was poor without TBAI (Table 1, entry 4); this result indicated that TBAI was indispensable for the reaction. However, the yield didn't improve when increase the catalyst loading to 20 mol% (Table 1, entry 5). The employment of the temperatures to 80 °C and 120 °C made the product yield decreased (Table 1, entries 6 and 7). Moreover, oxidants including di-*tert*-butyl peroxide (DTBP) and H_2O_2 were examined (entry 8-10), we were delighted to find that the yield of benzaldehyde had significant change by using H_2O_2 as the oxidant, especially with 8 equiv. of H_2O_2, afforded the desired product in 87% yield (Table 1, entry 12). Furthermore, we also investigated the efficiency of some other catalysts, such as I_2 and KI, provided the corresponding products in 83% and 62% yields (Table 1, entries 13 and 14). At last, solvents screening (MeCN, DMSO, DMF, H_2O, 1,4-dioxane) showed that DMAc is the optimal solvent for this transformation.

Table 1. Screening of reaction conditions.[a]



1a **2a**

Entry	Catalyst (mol%)	Oxidant (equiv)	Temp (°C)	Yield **2a** (%)[b]
1	TBAI (10)	TBHP (2)	100	45
2	TBAI (10)	TBHP (4)	100	50
3	TBAI (10)	TBHP (6)	100	22
4	TBAI (0)	TBHP (4)	100	11
5	TBAI (20)	TBHP (4)	100	29
6	TBAI (10)	TBHP (4)	80	32
7	TBAI (10)	TBHP (4)	120	37
8	TBAI (10)	DTBP (4)	100	trace
9	TBAI (10)	H_2O_2 (4)	100	59
10	TBAI (10)	H_2O_2 (6)	100	70
11	TBAI (10)	H_2O_2 (8)	100	87
12	I_2 (10)	H_2O_2 (8)	100	83
13	KI (10)	H_2O_2 (8)	100	62

[a] Reaction conditions: **1a** (1 mmol), catalyst, oxidant, DMAc (2 mL) for 24 h. [b] GC yield.

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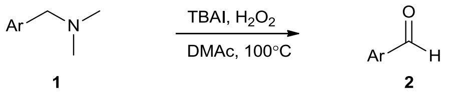
With the optimized reaction conditions in hand, we employed TBAI/H_2O_2 as the catalyst system to study the substrate scope of benzyl amines. As shown in Table 2, the reactions proceeded smoothly with a variety of functional groups on the benzene ring. The substrates bearing chloro-, bromo- at *para* position were compatible under standard conditions (Table 2, entries 2 and 3). Furthermore, nitro- and cyano- substitutions can give the desired aldehydes in good yields as well, especially cyano- group which can be transformed into the corresponding primary amides in the presence of oxidant (Table 2, entries 6 and 7). A comparable product yield to electron-withdrawing group was observed when the *para* position was substituted with electron-donating group, such as methoxy, *tert*-butyl moieties (Table 2, entries 9 and 10). However, substrates containing *para*-methyl group provided the corresponding product with slightly lower yield (Table 2, entry 8). It is noteworthy that those bearing *para*- and *meta*-substituted aryl groups worked better than *ortho*-substitution, probably due to the steric hindrance (Table 2, entries 3-5 and 10-12). We also tested the *para*-vinylphenyl substrate, which afforded the wished aldehyde in 50% yield (Table 2, entry 13). Furthermore, naphthalene and biphenyl substituents were also investigated and resulted in 66% and 68% yields respectively (Table 2, entries 14 and 15).

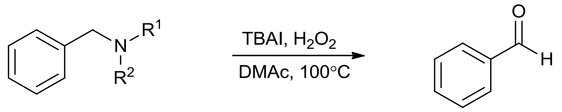
Table 2. Oxidative cleavage of benzylic C-N bond.[a]



Entry	1	Ar	Yield (%)[b]
1	**1a**	C_6H_5	85
2	**1b**	4-BrC_6H_4	66
3	**1c**	4-ClC_6H_4	57
4	**1d**	3-ClC_6H_4	58
5	**1e**	2-ClC_6H_4	52
6	**1f**	4-$NO_2C_6H_4$	61
7	**1g**	4-CNC_6H_4	62
8	**1h**	4-MeC_6H_4	40
9	**1i**	4-*t*-BuC_6H_4	66
10	**1j**	4-OMeC_6H_4	63
11	**1k**	3-OMeC_6H_4	59
12	**1l**	2-OMeC_6H_4	40
13	**1m**	4-VinylC_6H_4	50
14	**1n**	naphthyl	66
15	**1o**	biphenyl	68

[a] Reaction conditions: **1a** (1 mmol), TBAI (10 mol%), H_2O_2 (8 equiv), DMAc (2 mL), 100°C for 24 h. [b] Isolated yield.

Furthermore, primary and secondary benzyl amines which are represented by benzyl amine and *N*-methyl benzyl amine were studied as well (Scheme 1). Only trace amount of benzaldehyde was obtained from benzyl amine, while the reaction with *N*-methylbenzyl amine could afforded benzaldehyde in 50% yield.



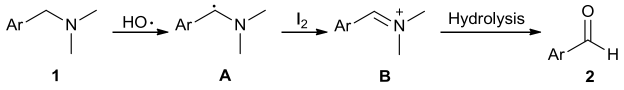
1p $R^1 = R^2 = H$
1q $R^1 = Me$, $R^2 = H$

trace
50% GC yield

Scheme 1. Formation of benzaldehyde from primary and secondary benzyl amines.

Based on these results, a possible reaction mechanism is shown in Scheme 2. First, decomposition of H_2O_2 by TBAI to generate hydroxy radical, which abstracts hydrogen of benzylic C-H bond and forms radical **A**. Radical **A** is then oxidized to iminium ion **B**, followed by hydrolysis to afford the final product **2**.

$$H_2O_2 + 2I^- \longrightarrow 2HO\cdot + I_2$$



Scheme 2. Proposed reaction mechanism.

Conclusions

In summary, a practical metal free strategy has been achieved for the synthesis of aromatic aldehydes using various *N,N*-dimethyl benzyl amines as starting materials. The reaction was mediated by an inexpensive and environmental friendly TBAI/H_2O_2 system and provided the benzaldehyde derivatives with moderate to good yields. Notably, this is the first example on oxidative cleavage of benzylic C-N bond under metal-free conditions.

General reaction procedure: Under air, in a 50 mL tube, TBAI (10 mol%), and a stirring bar was added. Then DMAc (2 mL), H_2O_2 (8 equiv.), substrate (1 mmol) were injected by syringe. Then close the tube and keep the final solution at 100 °C for 24 h. When the reaction was finished, the solvent was removed in vacuo, and the residue was purified by flash column (petroleum ether/ethyl acetate). All the products are commercially available.

Notes and references

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† Electronic Supplementary Information (ESI) available: [Analytic datas and NMR spectrums]. See DOI: 10.1039/b000000x/

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