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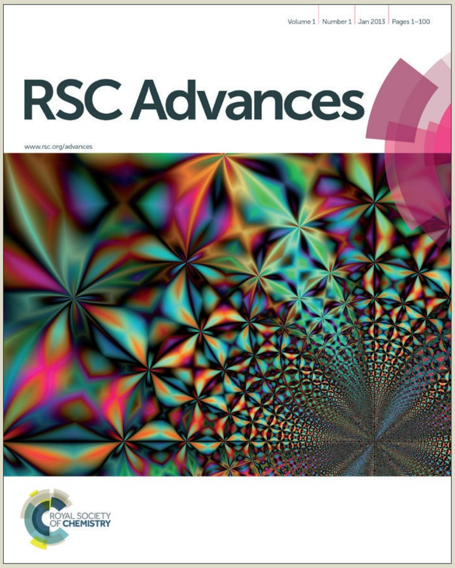

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Metal-Free TBHP-Mediated Oxidative Ring Openings of 2-Arylimidazopyridines Via Regioselective Cleavage of C–C and C–N Bonds

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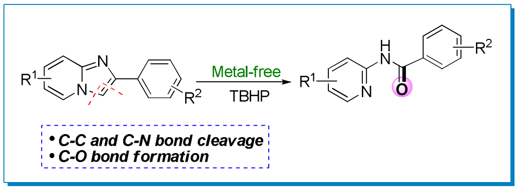
A highly regioselective TBHP-mediated ring openings of imidazopyridines via cleavage of C-C and C-N bonds has been achieved for the first time to afford *N*-(pyridin-2-yl)benzamides. Preliminary mechanistic investigations revealed that the present metal-free transformation involved a radical pathway, and the oxygen atom incorporated in the end products might derive from TBHP.

Carbon-carbon bonds are the most basic chemical bonds in organic molecules. The selective catalytic cleavage of C-C bonds for chemical transformations is a prime topic in synthetic organic chemistry and has become one of the most attractive and challenging tasks faced by researchers.[1] Traditionally, C-C bonds cleavage have been accomplished by *β*-carbon elimination,[2] decarbonylation reactions,[3] and oxidative addition reactions[4] *etc*. Recently, transition-metal-catalyzed selective C-C bonds cleavage has attracted considerable attention, and lots of excellent research achievements have been reported.[5] For example, copper-catalyzed aerobic selective C(CO)-C(alkyl) bond cleavage has been successfully achieved by Jiao,[6] Bi[7] and other groups.[8] On the other hand, the C-N bonds are omnipresent in organic compounds. Seeking mild and selective approaches for the cleavage of C-N bonds has become the hot topic of intensive studies.[9] Classical methods for C-N bond cleavage include the deprotection of *N*-protecting groups,[10] and the transformations of ammonium salts,[11] imidazoles,[12] triazenes,[13] diazonium salts[9b] and others.[14]

Although great advances of these C-C and C-N bonds cleavage transformations have been achieved, there are still certain limitations including harsh reaction conditions, and toxic and expensive metal salts in combination with oxidants which make it highly desirable to develop facile, efficient and transition-metal-free approaches to cleave C–C and C-N bonds. Futhermore, cleavage of both C-C and C-N bonds in a single organic transformation is an undoubtedly attractive but challenging objective. Nevertheless, until now, very few strategies for the cleavage of C-C and C-N bonds have been successfully developed in one molecule under one set of conditions.[15] In 2014, Laha and co-workers developed an elegant tandem oxidative conversion of 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines to phenazines via C-C and C-N bond cleavage under metal-free condtions.[15b] Especially, the direct transformation of relatively stable five-membered heterocyclics through C-C and C-N bonds cleavage in one step is still far from being addressed. Herein, for the first time, we describe a novel transition-metal-free oxidative C-C and C-N bonds cleavage of imidazopyridines leading to *N*-(pyridin-2-yl)benzamides using TBHP (*tert*-butyl hydroperoxide) as the oxidizing agent (Scheme 1).



Scheme 1 Synthesis of N-(pyridin-2-yl)benzamides via C-C and C-N bond cleavage

As shown in Table 1, we firstly chose 2-phenylimidazo[1,2-*a*]pyridine (**1a**) as the model substrate to explore the optimal reaction conditions. At the outset, when **1a** (0.4 mmol) and 4.0 equiv of TBHP were heated at 90 °C using toluene as the solvent under air atmosphene, the ring-open product **2a** could be obtained in 69% yield. Other oxidants such as DTBP, H_2O_2, and $K_2S_2O_8$ were surveyed at 90°C in 2 mL toluene, and TBHP was found to be the most effective oxidant (entries 1-5). Furthermore, the solvents, including DMF, H_2O, 1,4-dioxane, CH_3CN and DCE were tested using TBHP as the oxidant at 90 °C, and DCE provided the highest yield (73%) (entries 1, 6-10). Different reaction temperatures were also

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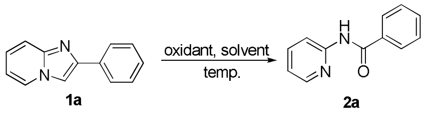
investigated (entries 10-12), showing that the best yield was obtained when the reaction was conducted at 80 °C (entry 11, Table 1). Additionally, different amounts of TBHP were attempted, and 4.0 equiv of TBHP was more suitable for the present transforamtion (compare entries 11, 13 and 14). Thus, the optimized reaction conditions for this ring-open conversation was: **1a** (0.4mmol), TBHP (4 equiv), in DCE at 90 °C under an air atmosphere for 18h.

Table 1 Optimization of the Conditions [a]

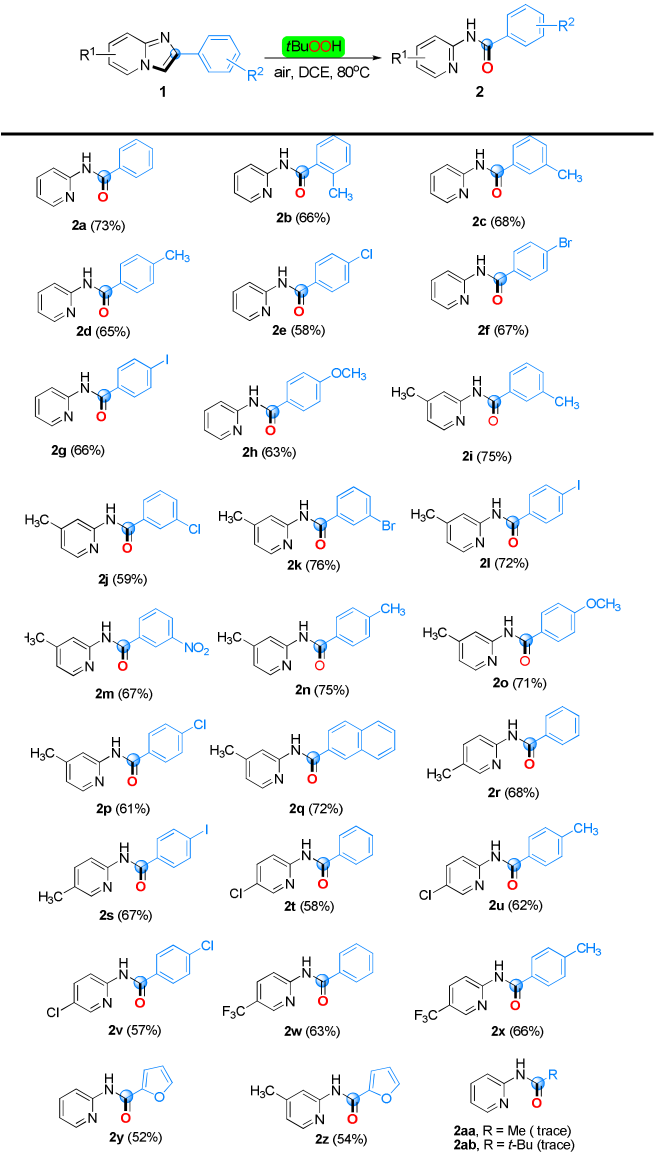


Entry	Oxidant	Solvent	Temp [°C]	Yield[b][%]
1	TBHP	Toluene	90	69
2	DTBP	Toluene	90	Trace
3	TBPB	Toluene	90	15
4	H_2O_2	Toluene	90	18
5	$K_2S_2O_8$	Toluene	90	Trace
6	TBHP	DMF	90	26
7	TBHP	H_2O	90	44
8	TBHP	1,4-Dioxane	90	31
9	TBHP	CH_3CN	90	65
10	TBHP	DCE	90	73
11	TBHP	DCE	80	73
12	TBHP	DCE	70	62
13	TBHP	DCE	80	71[c]
14	TBHP	DCE	80	56[d]

[a] Reaction conditions: **1a** (0.4mmol), TBHP (*tert*-butyl hydroperoxide 70 wt % in water.), solvent (2 ml) and reaction time (18 h). [b] Isolated yield. [c] In the presence of TBHP (5 equiv). [d] In the presence of TBHP (3 equiv).

With the optimized reaction conditions in hand, we next turned our attention toward the scope and limitation of the ring-open transformation, with the results summarized in Table 2. It was found that substrates bearing either electron-donating or electron-withdrawing groups on any aryl ring of the imidazopyridines could be applied to afford the corresponding products **2a**-**2z** in moderate to good yields. Strong electron-withdrawing substitutes such as -NO_2 and -CF_3 showed no obvious affect of the oxidative ring-open reaction (**2m**, **2w** and **2x**). This transformation displayed a satisfactory tolerance of halogen atom (**2f**, **2g**, **2j**, **2k**, **2l**, **2p** and **2s**), which could be used for further transformations through transition-metal-catalyzed cross-coupling reactions. Additionally, a naphthyl group could also participate participated in this transformation with a high reactivity (**2q**). Notably, when 2-furan imidazo[1,2-*a*]pyridines were used, the desired products of **2y** and **2z** were obtained in 52% and 54% isolated yields, respectively. Although this transformation was efficient, unfortunately, not all the imidazopyridines were compatible. For example, if 2-methylimidazo[1,2-*a*]pyridine **1aa** and 2-*tert*-butylimidazo[1,2-*a*]pyridine **1ab** were used as the substrates under the optimal reaction conditions, only a trace of product was obtained (**2aa** and **2ab**). The reason might be the electronic effect of the substrates influenced the stability of the transition state. Thus, further investigations to explore more powerful catalyst and oxidant was required. Some functional groups could be compatible in the present reactions, including methyl, methoxy, nitro, and trifluoromethyl.

Table 2 TBHP-mediated oxidative ring openings of imidazopyridines (**1**) leading to *N*-(pyridin-2-yl)benzamides (**2**) [a,b]



[a] Reaction conditions: **1a** (0.4mmol), TBHP (*tert*-butyl hydroperoxide 70 wt % in water.), solvent (2 ml), and reaction time (18 h). [b] Isolated yield.

In order to gain an insight into the reaction mechanism, several control experiments were performed with the results shown in Scheme 2. The reaction was suppressed remarkably when 2 equiv of BHT (2,6-*di*-*tert*-butyl-4-methylphenol), a well known radical-trapping reagent, was added into the present reaction system, which implied that the reaction might proceed via a free radical process (eq 1, Scheme 2). When the model reaction was performed under strictly moistureless conditions, the ring-opening products **2a**

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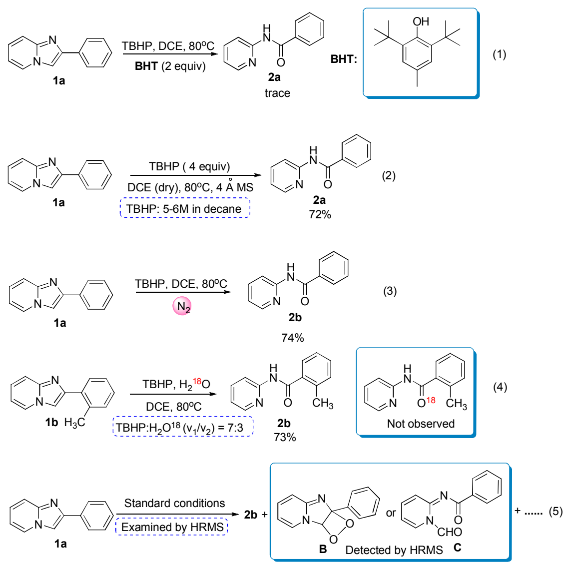
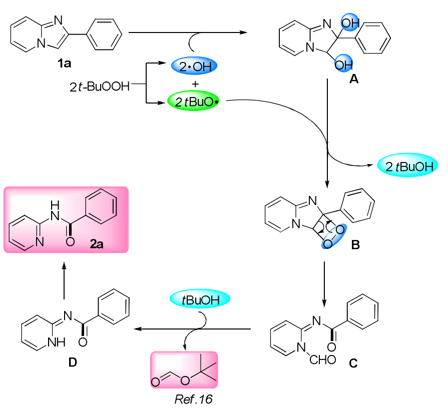
was obtained in 72% yield (eq 2, Scheme 2). Futhermore, the reaction can also proceed under a nitrogen atmosphere (eq 3, Scheme 2). Additionally, no $^{18}O_2$-**2a** was detected when $H_2{}^{18}O$ was introduced into in the reaction system (see Figure 1 in the Supporting Information) (eq 4, Scheme 2). These preliminary results indicated that the incorporated oxygen of the products might come from TBHP. Moreover, the reaction mixture was examined by HRMS after reation of **1a** with TBHP for a time, and peroxide intermediate (**B**) or (*Z*)-*N*-(1-formylpyridin-2(1*H*)-ylidene)benzamide (**C**) were found (see Figure 2 in the Supporting Information) (eq 5, Scheme 2).



Scheme 2 Investigations of the mechanism



Scheme 3 Plausible mechanism of the direct transformation

Although the mechanism for the cleavage pathway of present oxidative C–C and C–N bonds remains unclear, according to the previous report[16] and based on these preliminary experimental results mentioned above, a proposal mechanism would be herein presented (Scheme 3). Initially, TBHP was heated to generate the active racial *t*-BuO· and ·OH. Then, the addition of hydroxyl radical to **1a** resulted in the formation of the intermediate 1,2-diol **A**. Reaction of **A** with *t*-BuO· lead to an unstable four-membered peroxide intermediate **B**, which was possibly converted to **C**. Subsequently, a *tert*-butyl formate[16] was released from the intermediate **C** leading to **D** that could proceed the isomerization so as to afford the desired product **2a**. Further investigations on the more detailed mechanism are underway in our laboratory.

In conclusion, we have realized an unusual metal-free TBHP-mediated simultaneous cleavage of C-C and C-N bonds in 2-arylimidazopyridines. Preliminary mechanistic studies disclosed that the reactions might proceed via a radical pathway, and the oxygen atoms incorporated in the ring-opening products might derive from TBHP. The present protocol introduces a new model of C-C and C-N bonds cleavge in organic chemistry, although the detailed mechanism for the cleavage of C–C and C–N bonds remains unclear, of which further invetigations are ongoing in our laboratory.

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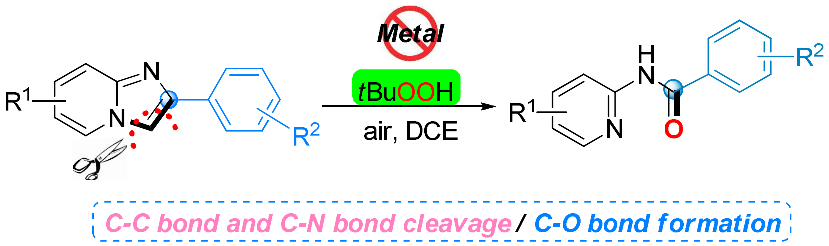

A highly regioselective TBHP-mediated ring openings of imidazopyridines via cleavage of C-C and C-N bonds has been realized for the first time to afford useful *N*-(pyridin-2-yl)benzamides under mild conditions.