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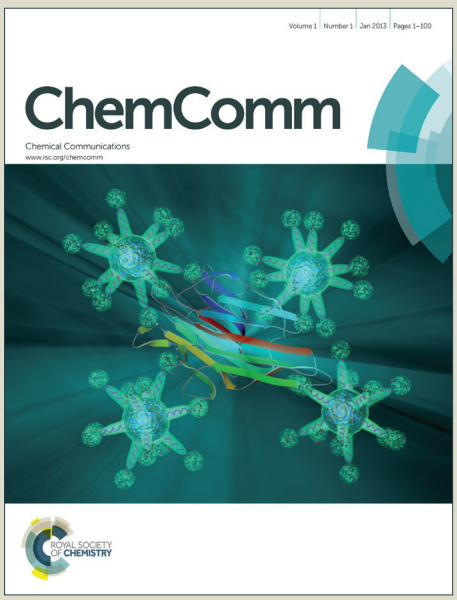

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ARTICLE TYPE

Oxidative Coupling of Methylamine with Aminyl Radical: Direct Amidation Catalyzed by I_2/TBHP with HCl

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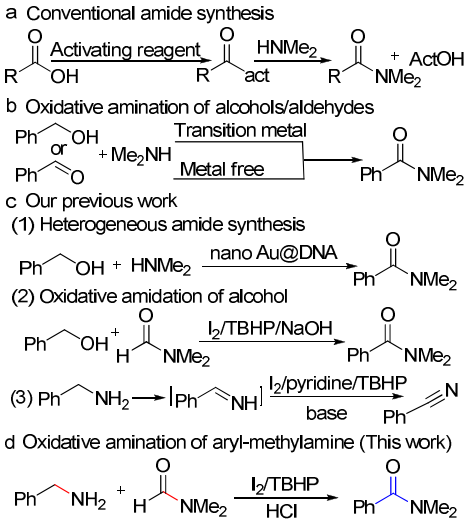
Oxidative coupling of methylamines with aminyl radical to construct amides was developed by virtue of I_2/TBHP catalyst under acidic condition via the two cleavages of the sp^3 C-N bond of aryl-methylamines and the sp^2 C-N bond of N-substituted formamides respectively. This transition-metal-free protocol provides a novel synthetic tool for the construction of N-substituted amide and a series of arylamides can be easily obtained with good yields.

Amides are prevalent structural units that are found in biologically relevant molecules, such as proteins, natural products, pharmaceuticals, and functional materials.[1] As a result, the construction of amides bond has attracted considerable attention and a series of efficient methods have been developed.[2,3] The traditional synthetic approach is the coupling of carboxylic acid with an amine via various activating reagents of carboxylic acid. Usually, a stoichiometric amount of activating reagents lead to low atom efficiency and great environmental pollution (Scheme 1, a).[2a] Other alternatives, such as the hydration of nitriles,[4] rearrangement of oximes,[5] and acylation of amines,[6] the cross-coupling of formamides with aryl/alkyl halides,[7] the modified staudinger reaction,[8] carbonylation of alkenes or alkynes,[9] have also proven to be efficient methods for the construction of the amide bond. In recent years, with the aim to construct an amide bond with a clean atom-economical manner, transition metal (Ru, Rh, Pd, Au and Cu) catalyzed oxidative coupling between alcohols/aldehydes and amines also provided elegant and direct access to amides.[10] Moreover, there are some new developments of metal-free oxidative coupling between alcohols/aldehydes and various amines sources (Scheme 1b).[11]

With the aim to construct an amide bond in a clean synthetic method, our group has developed two new protocols for the direct synthesis of benzamide from alcohol by using a Au/DNA nanohybrid catalyst (Scheme 1, c, (1)) and I_2/TBHP (tert-butyl hydroperoxide)/NaOH respectively (Scheme 1, c, (2)).[10f,11c] On the other hand, very recently, our group reported a novel protocol for cyanobenzene via an oxidation of arylmethylamine by using I_2-TBHP-pyridine catalyst (Scheme 1, c, (3)).[12a] Herein, as a logical extension of our two direct syntheses of benzamides, and encouraged by our previous work on I_2/TBHP catalysis,[12] we developed a metal-free oxidative coupling of aryl-methylamine with N-substituted formamide with good to excellent yield under mild condition. To the best of our knowledge, this is the first example of direct amidation via oxidative coupling of arylmethylamine with N-substituted formamides in one step.



Scheme 1 Typical pathways for the N,N-dimethyl-substituted amide synthesis.

Based on the reaction condition of our previous amidation of alcohol with N-substituted formamides (Scheme 1, c), initially, we focused in the I_2/TBHP/base catalyzed amidation of benzylamine (**1a**) with DMF.[11c] A series of bases including inorganic base such as NaOH, KOH, $LiOH{\cdot}H_2O$, K_2CO_3 and organic base such as pyridine and Et_3N were examined in the reaction. However, all of the attempts only got a trace amount of benzamide (**3aa**) (Table S1, entries 1-6). In the absence of any base, unexpectedly, the corresponding amide **3aa** was obtained in 38% yield when benzylamine was treated with DMF. This indicated that the base played a negative effect in this transformation. Therefore a variety of acids instead of base were added to the reaction mixture. For instance, HCl, HNO_3 and H_2SO_4 were added to the reaction respectively (Table S1, entries 8, 12, 13). As we expected, the reaction

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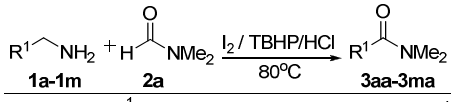
yield was increased up to 54% when 0.5mL of HCl (36 wt.% aqueous solution) were added into the reaction mixture. (Table S1, entry 8). Afterwards, different acids, such as HNO_3 and H_2SO_4, were screened in this reaction. However, the addition of other acids did not give a higher yield. This indicated that HCl was the best acid for this transformation. The optimization of the HCl addition showed that the 0.1 mL of HCl is the best addition amount in our reaction scale. Subsquently, the ratio of I_2 /TBHP /HCl was investigated, as shown in Table S2. The reaction gave the highest yield when 0.1 mL HCl was added to the reaction mixture in the presence of 25 mol% iodine and 4 equiv. of TBHP (Table S1, entry 12). More addition of HCl resulted in the decrease of the yield, perhaps due to the partial decomposition of amide. It was noted that other oxidants, such as $K_2S_2O_8$, H_2O_2, DTBP (ditertbutyl peroxide) m-CPBA and DDQ, were also employed in the reaction. No any improvement of this reaction was observed regardless of the addition of inorganic or organic oxidants, The experimental results indicated that only TBHP gave the highest reaction yield (Table S1, entries 15-19). Finally, the reaction temperature was also optimized. Enhancing the reaction temperature can promote the reaction while the reaction temperature beyond 80 °C would incur a lower yield due to the partial formation of benzoic acid from benzaldehyde. Therefore the optimal reaction temperature was 80 °C.

Table 1. Synthesis of amides from various benzylamines and DMF[a]



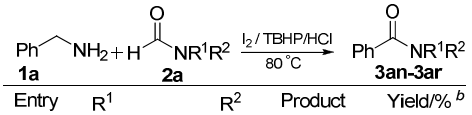
1a-1m **2a** **3aa-3ma**

Entry	R^1	Product	Yield/%[b]
1	C_6H_5	**3aa**	82
2	3-$CH_3C_6H_5$	**3ba**	72
3	4-$CH_3C_6H_5$	**3ca**	85
4	2-$CH_3OC_6H_5$	**3da**	65
5	4-$CH_3OC_6H_5$	**3ea**	77
6	4-$CF_3C_6H_5$	**3fa**	73
7	4-FC_6H_5	**3ga**	82
8	4-ClC_6H_5	**3ha**	75
9	2-BrC_6H_5	**3ia**	66
10	1-naphthaly	**3ja**	71
11	2-furyl	**3ka**	62
12	2-pyridyl	**3la**	65
13	2-thienyl	**3ma**	58

Reaction conditions: (a) benzylamine (107.1mg, 1 mmol), DMF (1 mL), I_2 (63.5 mg, 0.25 mmol), TBHP (360 mg, 4 eqiv., 70% cyclohexane solution), at 80 °C for 18 h. (b) isolated yield.

After the optimization, the best reaction condition was established as blow: I_2 (25 mol%) as the catalyst, TBHP (4 equivalents, 70% cyclohexane solution) as the oxidant, DMF (1mL) as both the nitrogen source and the solvent, concentrated HCl (0.1 mL) as the additive and the reaction being carried out at 80 °C for 18 h (Table 1). With the optimal reaction condition in hand, the generality of this direct amidation of aryl-methylamine was investigated as shown in Table 1. The reaction proceeded smoothly with different substrates to transform a wide range of N,N-dimethyl-substituted amides in moderate to good yields. It was found that electronic properties of benzylamines had little influence on the reaction (Table 1). For instance, either electron-donating substituted (Table 1, entries 2, 3, 5) or electron-withdrawing substituted benzylamines (Table 1, entries 6-8) afforded amides with good to excellent yields. In contrast, the steric effects of substituents had a great influence on the reaction. The reaction proceeded efficiently when meta- and para-substituted benzylamines were employed (Table 1, entries 2, 3, 5, 6, 7, 8). However, ortho-substituent had a negative effect on the transformation, which resulted in the lower yields (Table 1, entries 4 and 9). It is worth noting that halo-substituted benzylamines were well tolerated and the halo-substituents survive the raction (Table 1, entries 7, 8, 9). This provided the chance for further transformations to various molecules. On the other hand, the phenyl group in the benzylamine can be replaced by other aryl group. For example, when the phenyl group was replaced by a naphthyl group, the corresponding amide **3ma** can be obtained in 71% yield (Table 1, entry 10). Similarly, heteroaryl methylamine can be the reaction substrates in this reaction to afford the corresponding product with good yields (Table 1, entries 11–13).

Table 2. Reactions of benzylamine with N-substituted formamides.

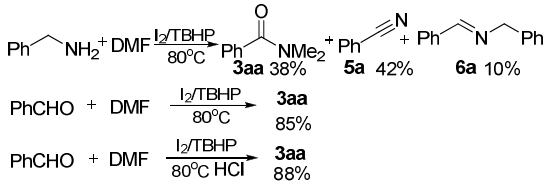


1a **2a** **3an-3ar**

Entry	R^1	R^2	Product	Yield/%[b]
1	Et	Et	**3an**	75
2	CH_3	H	**3ao**	63
3	Ph	H	**3ap**	72
4	piperidine	–	**3aq**	65
5	morpholine	–	**3ar**	58

(a) benzylamine (107.1mg, 1 mmol), N-substituted formamides (1 mL), I_2 (63.5 mg, 0.25 mmol), TBHP (360 mg, 4eqiv., 70% cyclohexane solution), at 80 °C for 18 h. (b) Isolated yield.

To further establish the general utility of this transformation, we examined the scope of N-substituted formamides. As shown in Table 2, when other N-substituted formamides were employed, the corresponding amides were also obtained in moderate to good yields. For example, N,N-diethyl-formamides with **1a** could give corresponding N,N-diethyl-benzamide **3an** in 75% yield. More importantly, the challenging substrate N-methylformamide and N-phenyl formamide worked well in the reaction to give the product **3ao** and **3ap** in a yield of 63% and 72% respectively (Table 2, entries 2 and 3) Also, the piperidine benzylamide and morpholine benzylamide can be easily obtained by virtue of this preparation with good yields (Table 2, entries 4 and 5). Normally they are very important intermediates in drug synthesis.



Scheme 2. Control experiments for the reaction mechanism.

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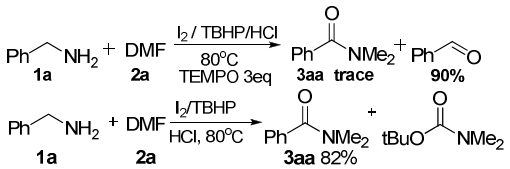
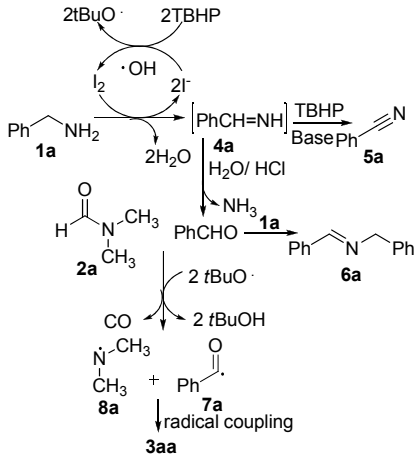
Next, we investigated the mechanism of the reaction. Firstly, we wanted to figure out the function of additive HCl. When benzylamine was treated with DMF in the absence of HCl, only 38% amide **3aa** was obtained. Nevertheless, the amide **3aa** was achieved in a yield of 85% when benzaldehyde was treated with DMF in the absence of HCl(Scheme 2). Under the standard condition, in contrast, benzaldehyde substrate can give the amide **3aa** in a yield of 88%. This indicates that the HCl played an important role in the oxidation of the methylamine rather than in the amidation step.



Scheme 3. Control experiments for the reaction mechanism**.**

When 3 equivalents of 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) was added, only a trace amount of amide **3aa** was detected while benzaldehyde was obtaind with 90% yield (Scheme 3). On the other hand, under the standard reaction condition, *tert*-butyl-N,N-dimethylcarbamate was detected on GC-MS, as shown in Figure S4. This indicated that the TBHP produced a radical to initiate the reaction via a cleavage of O-O bond.



Scheme 4. A proposed mechanism accounting for the formation of **3aa**.

On the basis of the control experiments and previous studies,[11d,12a] a possible reaction mechanism was proposed as shown in Scheme 4. Initially, benzylamine (**1a**) is oxidized to phenylmethanimine (**4a**) under catalysis of I_2/TBHP.[13,14] Then, I^- is oxidized to I_2 by *tert*-butyl hydroperoxide to realize the catalytic cycle. The imine **4a** is hydrolyzed into benzaldehyde catalyzed by HCl. Under the base condition or in the absence of HCl, the imine **4a** can be transformed into cyanobenzene **5** See Figure S2) and N-benzyl imine **6a** (See Figure S1). Simultaneously, the *tert*-butoxyl radical traps the H of benzaldehyde to form the benzoyl radical **7a.**[11c,15] Meanwhile, the aminyl radical **8a** is generated from DMF with the assistance of the generated *tert*-butoxyl radical,[16] subsequent cross-coupling of the benzoyl radical **7a** with the aminyl radical **8a** leads to formation of the corresponding amide **3aa.**

In conclusion, the first oxidative coupling of aryl-methylamines and N-substituted formamides has been developed. The reaction was catalyzed by I_2/ TBHP via the two cleavage of the sp^3 C-N bond of aryl-methylamines and the sp^2 C-N bond of N-substituted formamides. This transition-metal-free protocol provides a novel synthetic tool for the construction of N-substituted amide, especially N,N-dimethyl-substituted amides. Further studies to clearly understand the mechanism are ongoing in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental Details, characterization of catalysts and characterization of products. See DOI: 10.1039/b000000x/

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