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nBu$_4$NI-catalyzed unexpected amide bond formation between aldehydes and aromatic tertiary amines†

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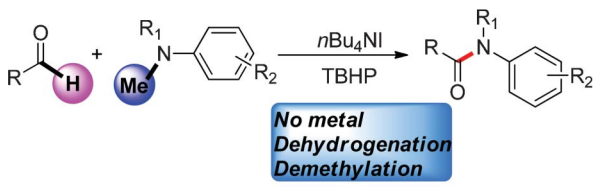
A novel and practical amide bond formation method has been developed without the need for any metals. This method provides a novel route for amide bond formation, in the presence of an nBu$_4$NI/TBHP catalyst system, from readily available aldehydes and aromatic tertiary amines.

The amide bond is one of the key structural units in a wide range of biological compounds, such as peptides, proteins, natural products and pharmaceuticals, and is also widely employed in synthetic polymers.[1] As a result, the development of efficient amide syntheses has attracted considerable interest. Conventionally, the amide bond is typically synthesized by acylation of amines (primary or secondary amines) with carboxylic acids or acid chlorides.[2] To avoid highly hazardous reagents and improve atom economy, many synthetic routes have been developed as alternative methods for amide synthesis, such as the aminocarbonylation of aryl halides,[3] modified Staudinger reaction,[4] Schmidt and Beckmann rearrangements,[5] direct amide synthesis from amines and alcohols,[6] amidation of nitriles,[7] rearrangement of oximes,[8] carbonylation of alkynes,[9] iodonium-promoted α-halo nitroalkane amine coupling[10] and C–H oxidative amidation.[11] Although great advances have been achieved in this field, there still remains some room for improvement. Direct oxidative amidation of aldehydes with amines is an attractive method with potential industrial applications. Although this process has achieved significant progress recently and a variety of reaction systems have been developed for this transformation, most of them are catalyzed by metals such as Ru, Y, Pd, Rh *etc.*,[12] so the transformation still suffers from drawbacks, such as using expensive transition metal catalysts. Recently, a new method for amide bond formation has been reported *via* C–H bond activation without metal by Wan[13a] and Wang.[13b] A similar method for the synthesis of α-ketoamides *via* amide bond formation without metal has also been reported by our group.[14] More recently, Li *et al.* reported the iron-catalyzed amidation of tertiary amines with aldehydes.[15] Herein, we report a new amide bond formation technique which is catalyzed by nBu$_4$NI, using TBHP as an oxidant, from readily available aldehydes and aromatic tertiary amines (Scheme 1). This method offers a new and alternative approach to amide bond formation without any metal catalysts.

Our investigation started with treating benzaldehyde (**1a**) and *N*,*N*-dimethylaniline (**2a**) under our previously reported catalyst system[14] to synthesize α-ketoamide through radical oxidative coupling. However, an unexpected compound *N*-methyl-*N*-phenylbenzamide (**3aa**) was obtained instead of our desired product α-ketoamide. This was an unexpected process, so we chose **1a** and **2a** as model substrates to optimize the reaction conditions. A series of reaction conditions are summarized in Table 1. As shown in Table 1, PhI(OAc)$_2$ was not an effective catalyst when using TBHP as the oxidant (Table 1, entry 1). No product was detected employing I_2 as catalyst (Table 1, entry 3). To our delight, KI displayed catalytic effect in this transformation with 42% product yield (Table 1, entry 2). A more soluble catalyst nBu$_4$NI was examined because KI has low solubility in DCE at 90 °C (Table 1, entries 4–11). We performed the reaction with a 1 : 1 (**1a** : **2a**) ratio of substrates to obtain a modest yield (Table 1, entry 4). When the amount of **2a** was increased, the reaction showed lower activation under the same conditions (Table 1, entry 5). Nevertheless, the reaction proceeded more smoothly when the amount of substrate **1a** was increased (Table 1, entries 6 and 7). We found **1a** reacted with **2a** at 90 °C in DCE to afford the desired product in 72% yield when the ratio was 2 : 1 (**1a** : **2a**) (Table 1, entry 8). However, continuing to increase the ratio of **1a** : **2a** was not favourable for this transformation (Table 1, entry 9). Among



Scheme 1 Synthesis of amides *via* aldehydes and aromatic tertiary amines.

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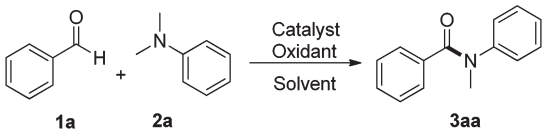
Table 1 Optimization of reaction conditions[a]



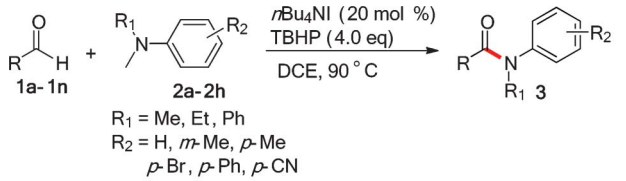
Entry	Catalyst (20 mol%)	Oxidant(4.0 eq)	Solvent	Yield (%)[b]
1	$PhI(OAc)_2$	TBHP	DCE	trace
2	KI	TBHP	DCE	42
3	I_2	TBHP	DCE	0
4[c]	nBu_4NI	TBHP	DCE	40
5[d]	nBu_4NI	TBHP	DCE	33
6[e]	nBu_4NI	TBHP	DCE	50
7[f]	nBu_4NI	TBHP	DCE	57
8[g]	nBu_4NI	TBHP	DCE	72
9[h]	nBu_4NI	TBHP	DCE	60
10	nBu_4NI	H_2O_2	DCE	0
11	nBu_4NI	DTBP	DCE	0
12	—	TBHP	DCE	0
13	nBu_4NI	—	DCE	0

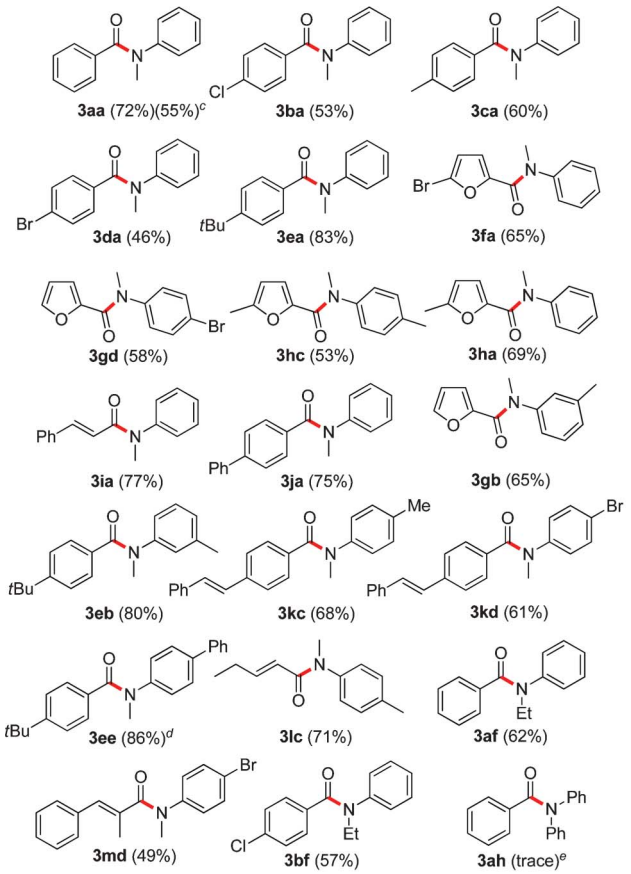
[a] Reaction conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), DCE (3 mL), under an air atmosphere, 10 h, 90 °C. TBHP: *tert*-butyl hydroperoxide 70% in water, DTBP: di-*tert*-butyl peroxide 98%, H_2O_2 30% in water. [b] Isolated yield. [c] **1a** : **2a** = 1 : 1. [d] **1a** : **2a** = 1 : 1.5. [e] **1a** : **2a** = 1.2 : 1. [f] **1a** : **2a** = 1.5 : 1. [g] **1a** : **2a** = 2 : 1. [h] **1a** : **2a** = 2.5 : 1.

the oxidants tested, H_2O_2 and DTBP showed no activation in this reaction (Table 1, entries 10 and 11). In addition, the reaction was unsuccessful in the absence of nBu_4NI or TBHP (Table 1, entries 12 and 13). It indicated that both catalyst and oxidant were important in this transformation.

With the optimal conditions in hand, the scope of the transformation was investigated and the results are summarized in Table 2. As shown in Table 2, the aldehydes with weak electron-withdrawing groups gave modest yields (Table 2, **3ba and 3da**). Unfortunately, aryl aldehydes which have strong electron-withdrawing groups, such as F, NO_2 and CF_3 were not suitable for this protocol (see ESI†). However, electron-rich aryl aldehydes all provided the corresponding amides smoothly. Electron-donating groups, such as *t*-Bu, Me and Ph attached to the phenyl rings of aryl aldehydes exhibited good reactivity (Table 2, **3ca, 3ea, 3ja and 3ee**). For example, when 4-(*tert*-butyl) benzaldehyde (**1e**) reacted with *N*,*N*-dimethylaniline (**2a**), amide **3ea** was obtained in 83% yield and [1,1′-biphenyl]-4-carbaldehyde (**1j**) also provided a high yield (75%). Likewise, product **3ee** could be obtained in 86% yield when 4-(*tert*-butyl) benzaldehyde (**1e**) reacted with amine **2e**. To our delight, furfural and its derivatives also provided the corresponding products in moderate yields (Table 2, **3fa, 3gd, 3hc, 3ha and 3gb**). Nevertheless, the investigation of other heteroaryl aldehydes, such as picolinaldehyde and 1*H*-indole-3-carbaldehyde in this reaction was unsuccessful (see ESI†). It is notable that a double bond in the substrates could be tolerated under the oxidative conditions. For example, cinnamaldehyde (**1i**), α-methylcinnamaldehyde (**1m**), *trans*-2-pentenal (**1l**) and (*E*)-4-styrylbenzaldehyde (**1k**) all performed well under the optimal conditions and gave the desired amides in moderate to good

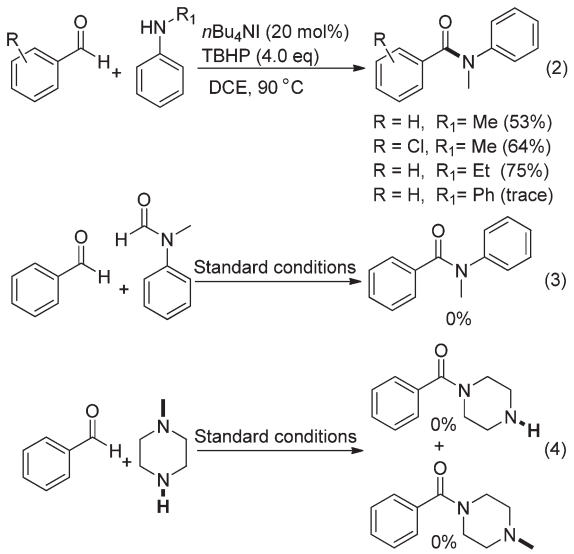
Table 2 nBu_4NI-catalyzed synthesis of amides from aldehydes with aromatic tertiary amines[a,b]



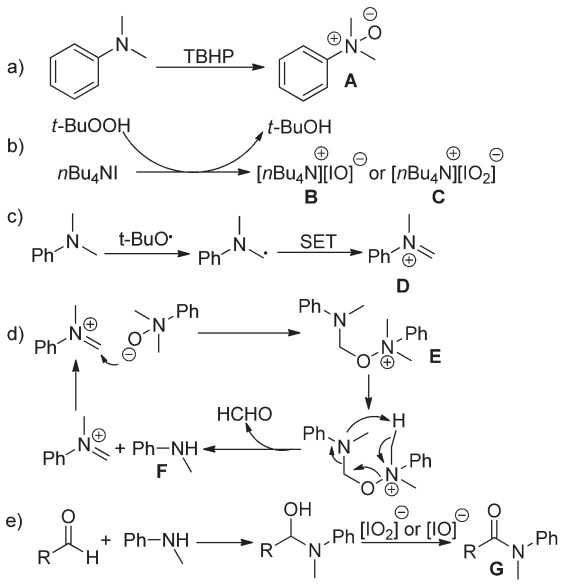


[a] Reaction conditions: aldehydes (2.0 mmol), amines (1.0 mmol), nBu_4NI (20 mol%), TBHP (4.0 mmol), DCE (3 mL), 90 °C, 10 h. [b] Isolated yield. [c] EtOAc instead of DCE as the solvent. [d] 5 h. [e] TBHP (6.0 mmol).

yields (49%–77%). Furthermore, as for aromatic tertiary amines, they could also proceed smoothly in the reaction if R_2 was an electron-donating group. However, no desired product was observed when R_2 was CN. When changing the *N*-substituent of amines, the transformation was still successful. For example, the desired products were obtained in moderate yields using *N*-ethyl-*N*-methylaniline (**2f**) as the substrate (Table 2, **3af and 3bf**). However, when R_1 was phenyl, it influenced the reaction efficiency remarkably (**3ah**). It indicated that the *N*-substituent (R_1) of the amines played an important role in the reaction. Unfortunately, *N*-methyl dialkyl tertiary amines, such as 1-methylpiperidin-4-one,



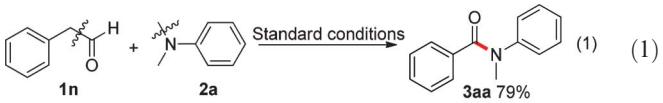
Scheme 2 nBu$_4$NI-catalyzed amide synthesis from aldehydes and *N*-methylaniline.



Scheme 3 Proposed preliminary mechanism.

4-methylmorpholine and 1-methylpiperidine were all ineffective in the reaction under the current conditions (see ESI†).

To our surprise, when 2-phenylacetaldehyde (**1n**) was investigated under the optimal conditions, it showed an interesting result (eqn (1)). Two carbons disappeared during this transformation and product **3aa** was obtained in good yield.



(1)

To gain insight into the mechanism of this novel reaction, some control experiments were performed. Gratifyingly, the reaction could also proceed to afford the desired amides under the optimal conditions when *N*-alkylaniline reacted with aldehydes (Scheme 2, eqn (2)). For example, *N*-methylaniline or *N*-ethylaniline reacted with benzaldehyde to obtain the corresponding products in 53% and 75% yields, respectively (Scheme 2, eqn (2)), but diphenylamine failed in this reaction (Scheme 2, eqn (2)). These investigations indicated that demethylation of the aromatic tertiary amine was involved in the reaction process when tertiary amines were used as substrates. To our disappointment, no product was observed when 1-methylpiperazine was used as the substrate to react with benzaldehyde. This experiment displayed that alkyl secondary amines were ineffective in this transformation (Scheme 2, eqn (4)). Otherwise, the reaction of *N*-methyl-*N*-phenylformamide with benzaldehyde provided no product under the optimized conditions (Scheme 2, eqn (3)). This result confirmed that the demethylation process was not *via* CO release as discussed in previous works (see ESI†).[16]

Based on the results of our investigation (see ESI† for more details) and Rosenau's and Scammells's studies about "*N*-demethylation of tertiary amine-*N*-oxides under oxidative conditions",[16a–c] a plausible mechanism is proposed in Scheme 3. In the first step (Scheme 3, eqn (a)), the aromatic tertiary amine is oxidized to its *N*-oxide **A**. The catalytic nBu$_4$NI is oxidized to species **B** or **C** and its mechanism has been proposed in previous work[17] (Scheme 3, eqn (b)). The intermediate **D** is formed *via* two SET processes which have been established in other reports.[16a–c,18] Then, *N*-oxide **A** reacts with intermediate **D** to form **E**, **E** produces intermediate **D** and secondary amine **F** *via* an autocatalytic deoxygenative demethylation process.[16a–c] In the end, the secondary amine **F** reacts with the aldehyde under oxidative conditions to form the final product **G** (Scheme 3, eqn (e)).

In summary, we have developed a novel method for the direct synthesis of amides, which are important structural units in many biological compounds, from aldehydes and aromatic tertiary amines. This transformation, catalyzed by nBu$_4$NI, includes the demethylation of tertiary amines and dehydrogenation of aldehydes in the absence of metal. Both substrates were cheap and readily available. Further investigations on this transformation are ongoing in our laboratory.

Acknowledgements

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