The *n*Bu$_4$NI catalysed oxidative benzoic acid amide formation from aryl acetaldehydes and amines in aqueous solution

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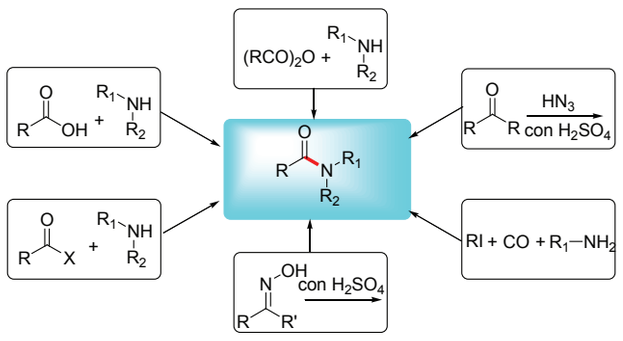
A metal-free amide synthesis from aryl acetaldehydes and secondary aromatic amines via a carbon degradation process using *n*Bu$_4$NI/TBHP system in aqueous solution is described. This protocol has not been reported previously. Both substrates are cheap and readily available.

Keywords: amine, phenylacetaldehyde, aqueous solution, metal-free amide synthesis

The amide bond is the key backbone in a wide range of biological compounds, such as proteins, peptides and pharmaceuticals and is also found applied in polymers.[1–4] As a result, the development of efficient amide syntheses has stimulated considerable attention. The amide bond is typically synthesised by acylation of amines (primary or secondary) with carboxylic acids or acid chlorides. This suffers from harsh conditions and the formation of byproducts (Scheme 1). Other synthetic methods have been developed for amide synthesis, such as a modified Staudinger reaction,[5] the aminocarbonylation of aryl halides,[6] Schmidt and Beckmann rearrangements,[7] direct amide synthesis from amines and alcohols,[8] amidation of nitriles,[9] rearrangement of oximes,[10] carbonylation of alkynes,[11] iodonium-promoted α-halo nitroalkane amine coupling and C–H oxidative amidation.[12,13] Although great advances have been achieved in this field, most of them are catalysed by metals such as, Ru, Pd and Rh,[14–16] so the transformations have not been applied effectively in industry. Recently, we have reported a new method for amide bond formation using aryl aldehydes and tertiary amines as substrates without the need of metals.[17] A similar method for the synthesis of α-ketoamides *via* amide bond formation without metals was also reported by our group.[18] This was more atom economic and made use of cheap and abundant starting materials. As a logical extension of these catalytic methods, we now report a new amide bond formation from aryl acetaldehydes and secondary aromatic amines which is catalysed by *n*Bu$_4$NI using TBHP as an oxidant in aqueous solution (Scheme 2). This method provides a novel approach to amide bond formation without any metal catalyst.

We first selected 2-phenylacetaldehyde (**1a**) and N-methylaniline (**2a**) as substrates to develop the reaction conditions in the absence of metals. The reaction conditions and results are summarised in Table 1.



Scheme 1 Overview of traditional methods of amide synthesis.

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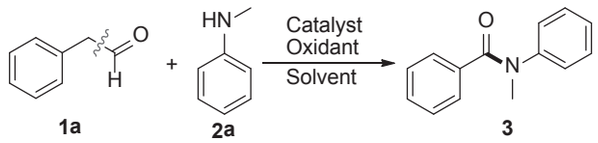


Scheme 2 Reaction sequence.

Treatment of a mixture of **1a** (120 mg, 1.0 mmol), **2a** (107 mg, 1.0 mmol), I_2 (0.2 mmol), TBHP (4.0 mmol) in 3 mL CH_3CN/H_2O at 90 °C in air for 15 h provided no product (Table 1, entry 1). KI displayed a catalytic effect in this transformation with 46% product yield (Table 1, entry 3). This was an unexpected result because the phenyl acetaldehyde lost a carbon in the process. We next tested CuI as catalyst under the same conditions, but the yield decreased to 26% (Table 1, entry 4). When *n*Bu$_4$NI was examined as catalyst, TBHP as oxidant, the desired product was increased to 60% yield in CH_3CN/H_2O (Table 1, entry 5). However, the yields decreased respectively in acetone/H_2O or DCE/H_2O using *n*Bu$_4$NI as catalyst (Table 1, entries 6 and 11). As shown in Table 1, *n*Bu$_4$NBr was not an effective catalyst using TBHP as oxidant (Table 1, entry 2). It showed that iodide anion played an important role in this reaction. Other oxidants such as DTBP, BPO, H_2O_2 and $K_2S_2O_8$ were also tested in this transformation under the same conditions, but none of them showed any activation (Table 1, entries 7–10).

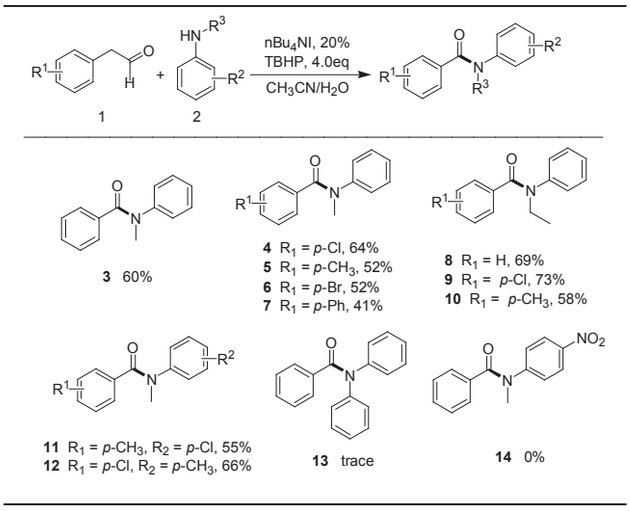
Under the optimised reaction conditions, the reactions between different aryl acetaldehydes and aromatic secondary amines were examined and the results are summarised in Table 2. As shown in Table 2, both electron-poor and electron-rich aryl acetaldehydes reacted efficiently with *N*-methylaniline (**2a**), *N*-ethylaniline (**2b**), *N*-4-dimethylaniline (**2c**) and 4-chloro-*N*-methylaniline (**2d**) to give the corresponding products (**3–12**) in moderate yields. For example, phenyl acetaldehyde (**1a**)

Table 1 Effect of solvents, catalysts and oxidants in the new reaction[a]

Entry	Catalyst	Oxidant	Solvent	Yield /%[b]
1	I_2	TBHP	CH_3CN/H_2O	Trace
2	*n*Bu$_4$NBr	TBHP	CH_3CN/H_2O	0
3	KI	TBHP	CH_3CN/H_2O	46
4	CuI	TBHP	CH_3CN/H_2O	26
5	*n*Bu$_4$NI	TBHP	CH_3CN/H_2O	60
6	*n*Bu$_4$NI	TBHP	Acetone/H_2O	35
7	*n*Bu$_4$NI	DTBP	CH_3CN/H_2O	0
8	*n*Bu$_4$NI	BPO	CH_3CN/H_2O	0
9	*n*Bu$_4$NI	$K_2S_2O_8$	CH_3CN/H_2O	0
10	*n*Bu$_4$NI	H_2O_2	CH_3CN/H_2O	0
11	*n*Bu$_4$NI	TBHP	DCE/H_2O	53

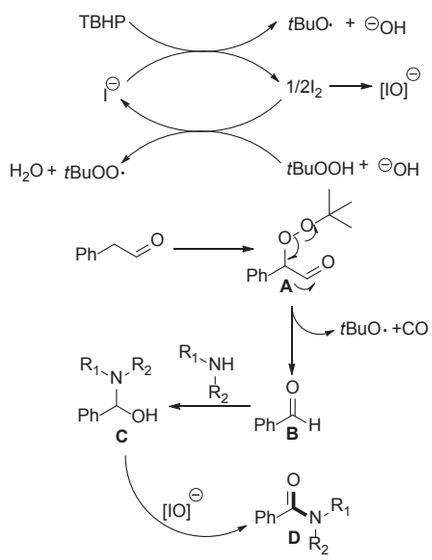
[a]Catalyst (20 mol%), **1a** (1.0 mmol), **2a** (1.0 mmol) and oxidant (4.0 equiv.) in 3 mL of the indicated solvent/H_2O (1:1) at 90 °C for 15 h. TBHP, tert-butyl-hydroperoxide, DTBP, tert-butyl-peroxide, BPO, benzoyl peroxide, DCE, 1,2-dichloroethane.
[b]Isolated yields.

Table 2 *n*Bu_4NI-catalysed amide bond formation of aryl acetaldehydes (**1**) with *N*-substituted anilines (**2**)



reacted with *N*-ethylaniline (**2b**) to form the amide product **8** in 69% yield. For *N*-substituted aniline, electron-withdrawing or electron-donating group on phenyl ring made no difference to the reaction. For example, *N*,4-dimethylaniline (**2c**) and 4-chloro-*N*-methylaniline (**2d**) reacted with different aryl acetaldehydes under the optimised conditions, giving similar yields. However, strong electron-withdrawing groups, such as NO_2, hindered the reaction severely and no product was observed (Table 2, **14**). In addition, the basicity of the aniline also influenced the transformation, for example, diphenylamine only gave a product in trace amounts (Table 2, **13**).

The use of *n*Bu_4NI as catalyst, TBHP as oxidant for amide bond formation has also been investigated in other reports,[19,20] but application in carbon degradation reaction, there is no relevant literature. Ishihara and other groups speculated on an alternative mechanism that involves hypoiodite as the actual oxidant.[21,22] We have attempted to explain the degradation process in this amide bond formation reaction. A possible mechanism is outlined in Scheme 3 on the basis of the earlier reports.[18,20] As shown in Scheme 3, we considered that the key intermediate **A** which formed by benzyl C–H bond of phenyl acetaldehyde reacting with *tert*-butylperoxy radical. It decomposes to generate benzaldehyde **B** which was then attacked by secondary amine to produce **C.** Finally, **C** was oxidised to the amide product.



Scheme 3 Probable mechanism.

In summary, we have developed a novel route to synthesise amides from aryl acetaldehydes and aromatic secondary amines. This protocol catalysed by *n*Bu_4NI *via* a carbon degradation process in aqueous solution has never been reported before. Both substrates are cheap and readily available. Further investigations on this method are continuing in our laboratory.

Experimental

All experiments were carried out using an ordinary flask in air. Aldehydes, aromatic secondary amines, *n*Bu_4NI and TBHP (70% in water) were purchased from commercial suppliers and used as received unless otherwise noted. All solvents and other commercially available reagents were purchased from Acros or TCI companies and used directly. Reactions were monitored by TLC (Qingdao Haiyang Chemical Co. Ltd. Silica gel 60 F254). Products were detected using a UV-Vis lamp (254 nm). Column chromatography was performed on Qingdao Haiyang Chemical Co. Ltd. Gel 60 (200–300 mesh). The ^1H and ^{13}C NMR spectras were obtained on a Bruker 400 MHz NMR Fourier transform spectrometer. ^1H NMR data was reported as: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR data was reported in terms of chemical shift (δ ppm) multiplicity and coupling constant (Hz). The spectra are referenced against the internal solvent ($CDCl_3$, δ_H = 7.26 ppm, ^{13}C = 77.0 ppm; DMSO-d6, δ 1H = 2.50 ppm, ^{13}C = 40.0 ppm). Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. ESI-MS spectra were recorded on a Bruker Esquire 3000. High resolution mass spectra (HRMS) were obtained on a Waters Micromass Q-Tof MicroTM instrument using the ESI technique.

Synthesis of **3–12***; general procedure*

An 50 mL vial was charged with magnetic stirring bar, arylacetaldehyde (**1**, 1.0 mmol), aromatic secondary amine (**2**, 1.0 mmol), *n*Bu_4NI (0.2 mmol), TBHP 70% in water (4.0 mmol), followed by CH_3CN/H_2O (3/3 mL). After stirring at 90 °C for 15 h, the reaction mixture was quenched with a saturated solution of Na_2SO_3 (to remove excess TBHP) and extracted with EtOAc (20 mL × 2). The combined organic phase was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure. The isolated yield was obtained by flash chromatography column on silica gel (gradient eluent of ethyl acetate in petroleum: 10–25%, v/v).

N-Methyl-N-phenyl-benzamide (**3**):[23,24] Yield 60%; yellow liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.32 (m, 2H), 7.21–7.26 (m, 6H), 7.04–7.19 (m, 2H), 3.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 144.9, 135.9, 129.6, 129.2, 128.7, 127.7, 126.9, 126.5, 38.41; HRMS $[M+1]^+$, calcd $C_{14}H_{14}NO$ 212.1075; found: 212.1077.

4-Chloro-N-methyl-N-phenyl-benzamide (**4**):[24] Yield 64%; yellow liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.28 (m, 4H), 7.14–7.21 (m, 3H), 7.04–7.06 (m, 2H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 144.7, 135.7, 134.3, 130.3, 129.4, 128.0, 126.9, 126.8, 38.5; HRMS $[M+1]^+$: calcd $C_{14}H_{13}ClNO$ 246.0686; found: 246.0685.

4-methyl-N-methyl-N-phenyl-benzamide (**5**):[23] Yield 52%; yellow liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14–7.28 (m, 5H), 7.05–7.07 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 3.51 (s, 3H), 2.28 (s, 3H); **^{13}C** NMR (100 MHz, $CDCl_3$) δ 170.7, 145.2, 139.8, 133.0, 129.1, 128.9, 128.4, 126.9, 126.3, 38.5, 21.3; HRMS $[M+1]^+$: calcd $C_{15}H_{16}NO$ 226.1232; found: 226.1240.

4-Bromo-N-methyl-N-phenyl-benzamide (**6**):[25] Yield 52%; colourless liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.33 (m, 2H), 7.27 (d, *J* = 6.4 Hz, 2H), 7.19 (t, *J* = 8.4 Hz, 3H), 7.05 (d, *J* = 8.4 Hz, 2H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 144.6, 134.8, 131.0, 130.4, 129.4, 126.9, 126.8, 124.1, 38.5; HRMS $[M+1]^+$: calcd $C_{14}H_{13}BrNO$ 290.0181; found: 290.0185.

Biphenyl-4-carboxylic acid methyl-phenyl-amide (**7**)[24]: Yield 41%; pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J*=7.2 Hz, 2H), 7.39–7.44 (m, 6H), 7.33–7.38 (m, 1H), 7.25–7.27 (m, 2H), 7.15–7.21 (m, 1H), 7.09–7.11 (m, 2H), 3.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 145.0, 142.3, 140.1, 134.7, 129.4, 129.3, 128.8, 127.7, 127.1, 126.9, 126.5, 126.4, 38.5; HRMS $[M+1]^+$: calcd $C_{20}H_{18}NO$ 288.1388; found: 288.1381.

N-Ethyl-N-phenyl-benzamide (**8**)[26]: Yield 69%; colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, *J*=7.6 Hz, 2H), 7.21–7.25 (m, 3H), 7.14–7.18 (m, 3H), 7.05 (d, *J*=7.2 Hz, 2H), 4.00 (q, *J*=7.2 Hz, 2H), 1.24 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 143.2, 136.3, 129.4, 129.1, 128.7, 127.9, 127.7, 126.6, 45.4, 13.0; HRMS $[M+1]^+$: calcd $C_{15}H_{16}NO$ 226.1232; found: 226.1234.

4-Chloro-N-ethyl-N-phenyl-benzamide (**9**)[26]: Yield 73%; colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.28 (m, 4H), 7.17–7.21 (m, 1H), 7.15 (d, *J*=7.2 Hz, 2H), 7.04 (d, *J*=7.2 Hz, 2H), 4.00 (q, *J*=7.2 Hz, 2H), 1.23 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 143.0, 135.5, 134.7, 130.2, 129.3, 128.0, 127.9, 126.9, 45.5, 12.9; HRMS $[M+1]^+$: calcd $C_{15}H_{15}ClNO$ 260.0842; found: 260.0840.

N-Ethyl-4-methyl-N-phenylbenzamide (**10**): Yield 58%; colourless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.26 (m, 5H), 7.05 (d, *J*=7.6 Hz, 2H), 6.95 (d, *J*=8.0 Hz, 2H), 4.02 (q, *J*=7.2 Hz, 2H), 2.26 (s, 3H), 1.23 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 143.5, 139.6, 133.4, 129.1, 128.8, 128.3, 127.9, 12.9; HRMS $[M+1]^+$: calcd $C_{16}H_{18}NO$ 240.1388; found: 240.1385.

N-(4-Chlorophenyl)-N,4-dimethylbenzamide (**11**): Yield 55%; brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.22 (m, 4H), 6.97–7.02 (m, 4H), 3.47 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 143.7, 140.1, 132.6, 131.9, 129.3, 128.8, 128.6, 128.0, 38.4, 21.4; HRMS $[M+1]^+$: calcd $C_{15}H_{15}ClNO$ 260.0842; found: 260.0848.

4-Chloro-N-methyl-N-(p-tolyl)benzamide (**12**): Yield 66%; white solid; m.p. 102–103 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J*=1.6 Hz, 6.4 Hz, 2H), 7.17 (dd, *J*=2.0 Hz, 6.8 Hz, 2H), 7.07 (d, *J*=8.4 Hz, 2H), 6.93 (d, *J*=8.0 Hz, 2H), 3.48 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 142.1, 136.6, 135.5, 134.4, 130.2, 129.9, 127.9, 126.6, 38.5, 20.9; HRMS $[M+1]^+$: calcd $C_{15}H_{15}ClNO$ 260.0842; found: 260.0840.

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