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General and efficient oxidative amidation of benzyl alcohols with amines using diacetoxyiodobenzene and TBHP

Yogesh B. Sutar, Saket B. Bhagat, Vikas N. Telvekar *

Department of Pharmaceutical Sciences & Technology, Institute of Chemical Technology, Matunga, Mumbai 400 019, India

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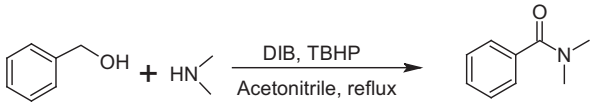
ABSTRACT

A facile oxidative coupling of alcohols and amines to construct amides was developed using DIB as a catalyst and aqueous *tert*-butyl hydroperoxide as an oxidant. Various secondary and tertiary amides were prepared in good yield utilizing inexpensive and readily available reagents under mild reaction condition. The reaction involved operational simplicity, metal free oxidation, and wide functional group tolerance as attractive features.

Amide is one of the most important functional groups found in polymers, fine chemicals, pharmaceuticals, and natural products.[1] The traditional synthetic approach used for amide formation involves the reaction of an amine with activated carboxylic acid derivatives[2] or coupling with carboxylic acids mediated by coupling reagents,[3] which suffers from several common drawbacks such as the use of highly hazardous reagents, harsh reaction conditions, toxicity issues, poor atom-efficiency, and generation of wastes that not only reduce process efficiency but also pose environmental problems. This necessitates the development of efficient methods for amide bond formation that circumvents these problems.

To overcome these limitations in amide synthesis, an array of novel methodologies have been developed, such as Beckmann rearrangement,[4] Staudinger reaction,[5] the Schmidt reaction,[6] amino carbonylation of haloarenes,[7] transamidation of primary amides,[8] oxidative amidation of aldehydes,[9] and aminolysis of esters.[10] Recently, oxidative amidation of alcohol using several transition-metal based homogeneous and heterogeneous catalysts like Zn,[11] Au-Pd/resin,[12] Au/DNA[13] and MnO_2(IV)–NaCN[14] afford an elegant alternative for direct access to amides. Also, metal free oxidative amidation of alcohol to amides using I_2/TBHP,[15] I_2/H_2O_2,[16] NaI/TBHP,[17] and NH_3/TBHP[18] have previously been reported. However, there still remains a challenge for the improvement of these reported methods, because the preparations of catalysts are time-consuming and precious metals have relatively high cost.



Scheme 1. Reaction between benzyl alcohol and aqueous dimethylamine in the presence of DIB and TBHP.

In the course of the continuous research of our group on developing novel efficient strategies, we decided to explore amide bond formation through aerobic oxidative coupling of alcohols and amines, using hypervalent iodine reagents, which offer the major advantages of mild reaction conditions, high efficiency, and a wide scope of substrates.

For our initial study, we carried out reaction between benzyl alcohol and aqueous dimethylamine in the presence of diacetoxyiodobenzene (DIB) and TBHP using acetonitrile as solvent under reflux condition for 10 h. The desired product *N*,*N*-dimethylbenzamide was isolated in moderate yield (Scheme 1).

Varying combinations of different iodine reagents and oxidizing agents were screened for this reaction and most of them provided moderate to good yield of *N*,*N*-dimethylbenzamide (Table 1).

To exploit the importance of the catalyst system, the oxidative amidation was carried out in the presence of only DIB (2.0 equiv, Table 1, entry 15), however, the reaction failed to afford the product in not more than 7% yield. It is also noteworthy to mention

* Corresponding author. Tel.: +91 22 3361 2213; fax: +91 22 3361 1020.
E-mail address: vikastelvekar@rediffmail.com (V.N. Telvekar).

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0040-4039/

Table 1
Effect of iodine reagents and oxidizing agents[a]

Entry	Iodine regent (mol %)	Oxidizing agent (eq)	% Yield[b]
1	I_2 (10)	TBHP (5)	30
2	PhI (10)	TBHP (5)	30
3	PhI (10)	Oxone (5)	NR
4	IBX (10)	TBHP (5)	45
5	DMP (10)	TBHP (5)	46
6	DIB (10)	Benzyl peroxide (5)	17
7	DIB (10)	H_2O_2 (5)	10
8	DIB (10)	Oxone (5)	7
9	DIB (10)	*m*-CPBA (5)	8
10	DIB(10)	TBHP (5)	61
11	DIB(20)	TBHP (5)	76
12	DIB (20)	TBHP (8)	86
13	DIB (20)	TBHP (10)	87
14	DIB (25)	TBHP (8)	85
15	DIB (2 equiv)	—	7
16	—	TBHP (10)	20

[a] Reaction conditions: 1.0 mmol of benzyl alcohol, 2.5 equiv aqueous *N*,*N*-dimethylamine, oxidizing agent, iodine reagent in acetonitrile at reflux temperature.
[b] Isolated yield.

that in the presence of only TBHP (10.0 equiv, Table 1, entry 16), even after 10 h, the oxidative amidation failed to yield the product above 20%. Thus, it was concluded that a combination of both, the catalyst and the oxidant, in an adequate ratio is essential to obtain the desired amide product.

Thus after analyzing different reaction conditions, it was observed that in the case of secondary amines, the desired product was obtained in good yield when 8 equivalent of TBHP and a catalytic amount (20 mol %) of diacetoxyiodobenzene were used (Table 1, entry 12).

We also attempted different solvents such as water, toluene, ethanol, 1,4-dioxane, and tetrahydrofuran. However, all these reactions gave lower yields than that in acetonitrile. Thus, it was observed that 20 mol % DIB, 8 equiv of TBHP in acetonitrile at reflux temperature was the optimal reaction condition to afford the desired amide in good yield. It was interesting to know that under similar conditions, when primary amine (phenylethylamine) was reacted with benzyl alcohol, the desired product *N*-phenethylbenzamide was obtained in lower yield (52%). However, changing

Table 2
Synthesis of various amides using DIB and THBP[a]

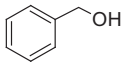
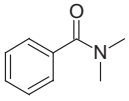
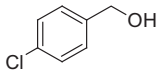
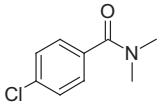
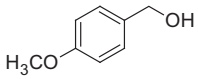
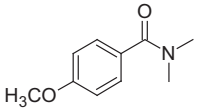
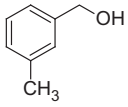
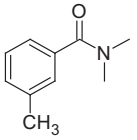
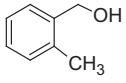
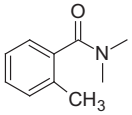
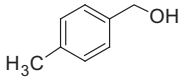
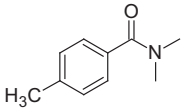
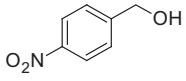
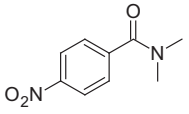
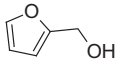
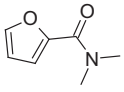
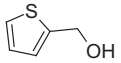
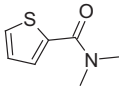
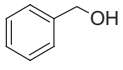
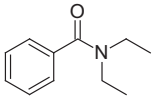
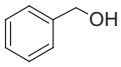
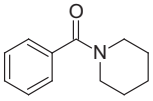
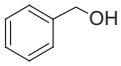
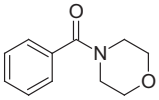
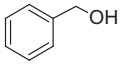
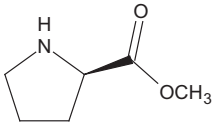
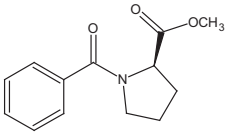
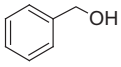
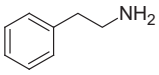
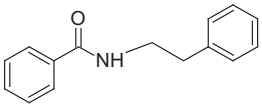
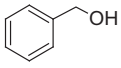
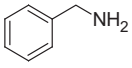
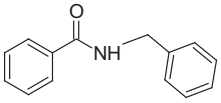
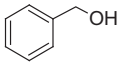
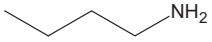
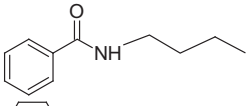
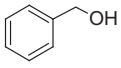
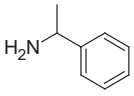
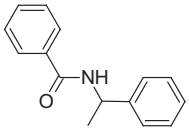
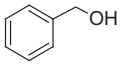
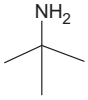
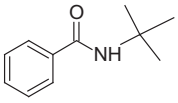
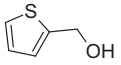
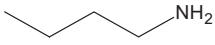
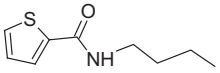
Entry	Aryl alcohol	Amine	Product	Yield[b] (%)
1				86
2				88
3				78
4				80
5				65
6				80
7				83
8				72
9				79
10				84

Table 2 (*continued*)

Entry	Aryl alcohol	Amine	Product	Yield[b] (%)
11				88
12				88
13				81
14[c]				74
15[c]				69
16[c]				74
17[c]				67
18[c]				69
19[c]				65

[a] Reaction conditions: 1 mmol of aryl alcohol, 2.5 mmol of amine, 8 mmol of THBP, and 20 mol % DIB in acetonitrile at 80 °C.
[b] Isolated yields after column chromatography and structures were confirmed by comparison of IR, ^{1}H NMR, and M.P. with literature reports.[17,21]
[c] Water was used as a solvent instead of acetonitrile (entries 14–19).

the solvent from acetonitrile to water, afforded the desired product in good yield (74%).

To extend the scope and generality of this catalytic system, the above optimized conditions were used for preparation of a variety of substituted amides and results are summarized in Table 2.[19]

Various aromatic amides, bearing electron-withdrawing and donating groups on the aromatic rings, could be obtained in good to moderate yields from the corresponding aromatic alcohols (Table 2, entries 2–7). It was also observed that the ortho substituted compound shows a lower yield, than corresponding *meta* and *para* substituted derivatives, may be due to the presence of steric hindrance (Table 2, entry 5). Heteroaromatic alcohols, such as 2-thenyl alcohol and furfuryl alcohol, also reacted with aqueous dimethylamine in the presence of DIB and TBHP to give the corresponding N,N-dimethyl heteroaromatic amides in good to moderate yields (Table 2, entries 8 and 9). The secondary cyclic amines, like morpholine and piperidine, also gave the desired products in good yield (Table 2, entries 11 and 12).

The reaction of benzyl alcohol with primary amines, such as phenylethylamine, *n*-butylamine, α-methylbenzylamine, *tert*-butylamine, and benzylamine, in the presence of DIB and TBHP in water was then carried out. The results indicate that the *N*-alkyl/alkylaryl benzamides from primary amines were obtained in moderate to good yields (Table 2, entries 14–19). Compound like L-proline also underwent amidation to provide the corresponding amides (Table 2, entry 13) in good yield.

It was observed that when aromatic amines, like aniline, were reacted with benzyl alcohol, the corresponding amides were obtained in a very low yield (20–25%). It is also noted that *S*-1-phenylethylamine undergoes a similar transformation without epimerization. This non-epimerization of L-proline and *S*-1-phenylethylamine, in the corresponding amides, was confirmed by optical rotation data, which matches with the literature data.[20]

In conclusion, DIB and TBHP have been explored as an efficient organocatalyst for oxidative amidation of various aryl alcohols, bearing electron-withdrawing and electron-donating groups on the aromatic rings, with amines for the synthesis of amides in good yields. The present reaction is simple and environmentally benign, and generates little waste. These novel cost-effective amide formation reactions provide practical alternatives for the synthesis of amides under mild conditions.

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19. *General procedure for the oxidative amidation of aryl alcohol with secondary amine:* To a mixture of aryl alcohol (1.0 mmol), appropriate amine (2.5 mmol) and TBHP (70 wt % in H_2O, 8.0 mmol) in acetonitrile (5 mL), was added DIB (0.2 mmol, 20 mol %) at room temperature. The reaction was allowed to stir at reflux temperature for 5–6 h. After the reaction was complete, as indicated by TLC, the mixture was cooled to room temperature. The volatiles were removed under reduced pressure and 10 mL saturated solution of $NaHCO_3$ was added. The mixture was extracted with ethylacetate (3×10 mL). The combined organic phases were dried with Na_2SO_4 and evaporated under vacuum. Purification of the residue by column chromatography (petroleum ether/EtOAc) afforded the desired amide.
N,N-Dimethylbenzamide (Table 2, entry 1): Mp 44–46 °C (Lit. 21 42–44 °C); IR (KBr): 3057, 2998, 2934, 2854, 1631, 1431, 1271, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.00 (bs, 3H), 3.15 (bs, 3H), 7.40–7.51 (m, 5H); ^{13}C NMR ($CDCl_3$, TMS): δ = 35.4, 39.7, 127.1, 128.4, 129.8, 136.2, 171.1; HRMS: calcd for $C_9H_{11}NO$: 149.0841, found 149.0845.
4-Methoxy-N,N-Dimethylbenzamide (Table 2, entry 3): Mp 40–42 °C (Lit. 21 41–42 °C); IR (KBr): 2936, 1615, 1574, 1491, 1449, 1392, 1300, 1250, 1176, 1083, 1027, 843, 764, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.01 (bs, 6H), 3.81 (s, 3H), 6.70–6.91 (m, 2H), 7.39–7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS): δ = 37.4, 38.1, 55.5, 113.6, 128.1, 128.8, 160.5, 171.9; HRMS: calcd for $C_{10}H_{13}NO_2$: 179.0946, found 179.0952.
N,N-Dimethylthiophene-2-carboxamide (Table 2, entry 9): Mp 42–45 °C (Lit. 21 44–45 °C); IR (KBr): 2998, 2934, 1631, 1431, 1271, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.17 (bs, 6H), 7.02–7.05 (m, 1H), 7.36–7.38 (m, 1H), 7.45–7.52 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS): δ = 29.80, 31.1, 126.6, 128.9, 129.5, 138.2, 164.5; HRMS: calcd for C_7H_9NOS: 155.0405, found 155.0411.
Morpholino(phenyl)methanone (Table 2, entry 12): Mp 66–69 °C (Lit. 21 68–70 °C); IR (KBr): 2979, 2901, 2859, 1626, 1426, 1361, 1300, 1271, 1111, 1073, 1020, 933, 840, 796, 736, 712, 592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.37–3.85 (m, 8H), 7.48 (m, 5H); ^{13}C NMR ($CDCl_3$, TMS): δ = 42.4, 48.2, 66.7, 76.84, 77.16, 77.48, 127.3, 128.8, 129.6, 135.1, 170.5; HRMS: calcd for $C_{11}H_{13}NO_2$: 191.0946, found 191.0947.
N-Phenethylbenzamide (Table 2, entry 13): Mp 115–117 °C (Lit. 21 115–116 °C); IR (KBr): 3342, 2922, 1640, 1632, 1547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.65 (m, 2H), 3.74 (m, 2H), 6.30 (bs, 1H), 7.27–7.75 (m, 10H); ^{13}C NMR ($CDCl_3$, TMS): δ = 35.8, 40.9, 126.4, 127.9, 128.3, 128.8, 129.2, 131.9, 134.1, 139.8, 170.2; HRMS: calcd for $C_{15}H_{15}NO$: 225.1154, found 225.1234.
N-Butylbenzamide (Table 2, entry 14): Mp 40–42 °C (Lit. 21 39–41 °C); IR (KBr): 3310, 2957, 2931, 2871, 1635, 1577, 1540, 1435, 1376, 1074, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.98 (t, 3H), 1.30–1.45 (m, 2H), 1.53–1.62 (m, 2H), 3.40–3.46 (m, 2H), 7.23 (bs, 1H), 7.36–7.39 (m, 2H), 7.46–7.49 (m, 1H), 7.74–7.76 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS): δ = 13.6, 20.1, 31.6, 39.7, 126.8, 128.3, 131.1, 134.7, 167.5; HRMS: calcd for $C_{11}H_{15}NO$: 177.1154, found 177.1204.
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