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Oxidative Amidation of Aldehydes and Alcohols with Primary Amines Catalyzed by KI-TBHP

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Oxidative amidation of aldehydes and alcohols with amines to afford the corresponding amides in excellent yields and *ee* values over 98 % is achieved by using a catalytic amount of KI in combination with TBHP as the external oxidant. This method avoids the use of expensive and/or air-sensitive reagents.

Introduction

Simple and convenient methods for the construction of amide (-CONH-) units are highly desirable in synthetic organic chemistry.[1] These motifs play a significant role in biological systems as well as in important molecules in the fields of pharmaceuticals, natural products, and polymers.[2] Conventional methods for the synthesis of amides involve reactions between carboxylic acids or their activated analogues like acyl chlorides, anhydrides, azides, or an active ester and amines.[3] Alternate methods include metal-catalyzed aminocarbonylation,[4–6] modified Staudinger reaction,[7] acid-promoted Schmidt reaction,[8] coupling of carboxylic acids with isocyanide,[9] and oxidation of imines to amides via an oxaziridine.[10] Recently, Rovis' and Bode's group reported amidation with N-heterocyclic carbene (NHC) catalysts.[11] Another alternative approach, which is quite attractive from the economical and green chemistry points of view, is the oxidative amidation of aldehydes [Equation (1)].

$$\mathrm{RCHO} \quad + \quad \mathrm{R'NH_2} \quad \xrightarrow[\text{catalyst}]{\text{oxidant}} \quad \mathrm{RCONHR'} \quad + \quad \mathrm{H_2O} \tag{1}$$

Few reports adapting the above strategy have appeared in the literature.[12–17] Among them, the most recent examples are: ruthenium- and rhodium-catalyzed oxidative amidation of aldehydes with secondary amines,[14] copper-catalyzed oxidative amidation of aldehydes with hydrochloride salts of primary amines in the presence of base and $AgNO_3$ as an additive,[15] catalytic amidation of aldehydes with secondary amines by lanthanum complexes,[17] and a metal-free oxidative amidation of aldehydes with secondary amines achieved solely by an oxidant (TBHP).[16] Recently, the Milstein group reported the amidation of alcohols and amines via aldehyde intermediates by using Ru-PNN pincer catalysts.[18] Despite the rapid progress made in catalytic amidation reactions, there are still shortcomings in the adaptability of these methodologies to scale-up. For example, most of the catalysts reported are either expensive or involve a multistep synthesis. Moreover, stoichiometric amounts of bases and sensitive reagents are employed.

Molecular halogens and related reagents are well known oxidizing agents with simple operation and low cost. Among the several reagents reported in literature, molecular iodine is an attractive candidate as it is cheap, readily available, and less toxic than molecular bromine or chlorine. Several reports appeared recently on the use of iodine for various organic transformations.[19] Furthermore, molecular iodine is efficiently utilized for the oxidation of alcohols and aldehydes into their corresponding esters.[20] One of the limitations of these procedures is the use of stoichiometric amounts of iodine and a base, which could lead to the generation of excessive amounts of waste. We have recently observed a simple and mild procedure for the facile oxidative esterification of aldehydes and alcohols by using a catalytic amount of KI in combination with TBHP as an external oxidant [Equation (2)].[21]

$$\mathrm{RCHO} \quad + \quad \mathrm{R'OH} \quad \xrightarrow[\text{solvent, reflux}]{\text{KI, TBHP}} \quad \mathrm{RCOOR'} \quad + \quad \mathrm{H_2O} \tag{2}$$

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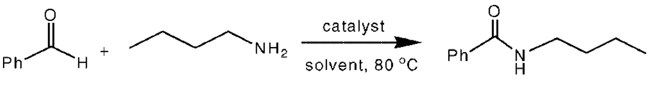
Results and Discussion

Encouraged by these results, we extended the methodology for much more interesting and challenging oxidative amidations of aldehydes with amines. The results are presented here.

Initial optimization studies were carried out by treating benzaldehyde with butylamine under different conditions. The results are tabulated in Table 1. The blank reaction with KI and without an oxidant provided imine as the sole product, whereas the reaction with TBHP resulted in 15% of the required amide. Under the similar conditions 5 mol-% KI and TBHP provided 75% of amide. Organic solvents like acetonitrile provided lower conversions.

Table 1. Optimization of oxidative amidation for the synthesis of amide **1a**.[a]



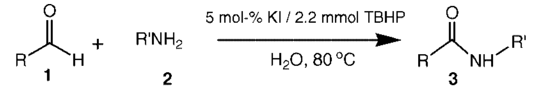
1a

Entry	Catalyst [mmol]	Oxidant [mmol]	Solvent	Yield [%][b]
1	KI [0.05]	–	H_2O	–[c]
2	–	TBHP [2.2]	H_2O	15
3	KI [0.05]	TBHP [2.2]	H_2O	75
4	KI [0.05]	TBHP [1.5]	H_2O	55
5	KI [0.05]	H_2O_2 [2.2]	H_2O	–[c]
6	KI [0.05]	TBHP [2.2]	CH_3CN	45
7	–	TBHP [2.2]	CH_3CN	11

[a] Reaction conditions: benzaldehyde (1 mmol), butylamine (1.2 mmol), solvent (3 mL), 80 °C, 15 h. [b] Isolated yield. [c] The imine is the main product.

To explore the generality and scope of the reaction, the oxidative amidation reaction was carried out with various aldehydes and amines under the optimized reaction conditions. The results are shown in Table 2. All the aromatic aldehydes exhibited good reactivity. In general, aromatic aldehydes with electron-donating groups showed higher activity than their electron-withdrawing counterparts (Table 2, entries 1–10). Moderate to good yields were also observed for different amine sources (Table 2, entries 11–16). In case of aliphatic aldehydes, the reaction between octanal and *n*-butylamine was not straightforward, and the required amide was obtained in a lower quantity (<20%) (Table 2, entry 17). Whereas a moderate yield (49%) was observed for the reaction between cyclohexanecarbaldehyde and *n*-butylamine (Table 2, entry 18). The reaction between phenylacetaldehyde and *n*-butylamine led to a mixture of *N*-butylbenzamide and *N*-butyl-2-phenylacetamide (Table 2, entry 19). Our attempts with the reactions between aromatic aldehydes and benzylamine derivatives were not successful and usually led to mixtures of products.[22]

Table 2. KI-TBHP-catalyzed oxidative amidation of aldehydes with amines.[a]

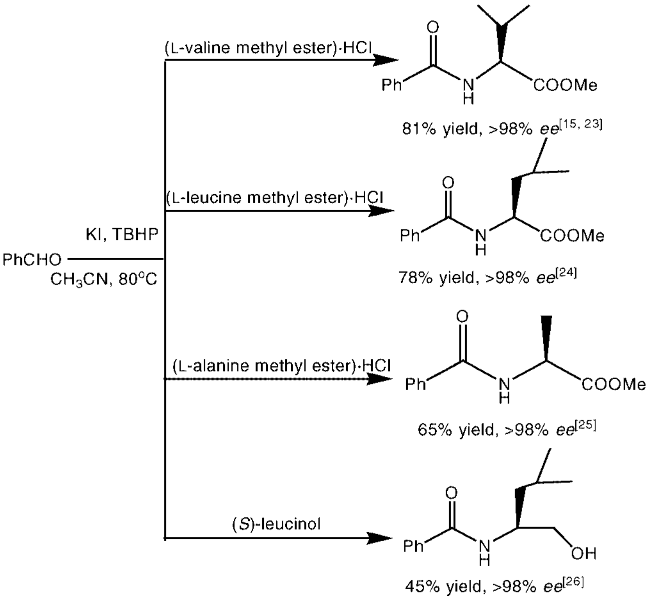


Entry	R	R'	Amide	Yield [%][b]
1	Ph	*n*Bu	**3a**	76
2	*p*-NO_2-C_6H_4	*n*Bu	**3b**	32
3	*p*-Cl-C_6H_4	*n*Bu	**3c**	77
4	*p*-B-rC_6H_4	*n*Bu	**3d**	44
5	*p*-F-C_6H_4	*n*Bu	**3e**	72
6	*o*-F-C_6H_4	*n*Bu	**3f**	63
7	*p*-Me-C_6H_4	*n*Bu	**3g**	80
8	*p*-*i*Pr-C_6H_4	*n*Bu	**3h**	50
9	*p*-MeO-C_6H_4	*n*Bu	**3i**	80
10	2-naphthyl	*n*Bu	**3j**	71
11	Ph	octyl	**3k**	51
12	Ph	cyclohexyl	**3l**	63
13	Ph	*i*Pr	**3m**	53
14	Ph	*t*Bu	**3n**	42
15	Ph	morpholyl	**3o**	63
16	Ph	piperydyl	**3p**	61
17	octyl	*n*Bu	**3q**	18[c]
18	cyclohexyl	*n*Bu	**3r**	49[c]
19	$PhCH_2$	*n*Bu	**3s**	25[d]

[a] Reaction conditions: Aldehyde (1 mmol), primary amine (1.2 mmol), TBHP (2.2 mmol), KI (0.05 mmol) in H_2O (3 mL), 80 °C, 15 h. [b] Isolated yield. [c] Yields based on GC. [d] 30% of the amide corresponding to benzaldehyde was also observed by GC.

To widen the scope of oxidative amidation to chiral systems, benzaldehyde was treated with L-valine methyl ester hydrochloride under the optimized conditions (Table 1, entry 3). ^{1}H NMR analysis of the crude reaction mixture shows only 8% of product. However, changing the solvent from water to acetonitrile improved product formation significantly (54%). Furthermore, increasing the catalyst loading to 20 mol-% yielded 81% of the coupled product with >98% enantioselectivity. Similarly, reactions with L-leucine, L-alanine methyl ester hydrochlorides and (*S*)-leucinol provided the coupled products in reasonable yields with excellent enantioselectivities (Scheme 1).

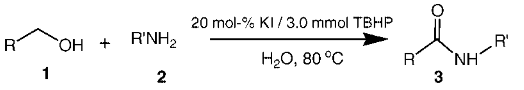
We have further investigated the applicability of the present catalytic system to benzyl alcohol derivatives. The results are shown in Table 3. Moderate yields were observed with benzyl alcohol and *p*-methoxybenzyl alcohol, whereas

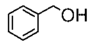
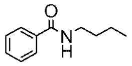
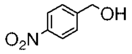
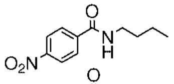
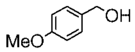
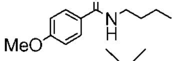
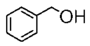
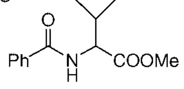


Scheme 1. Reaction between benzaldehyde and amino acid derivatives.

a low yield (10%) was obtained with *p*-nitrobenzyl alcohol. The direct coupling of benzyl alcohol with (L-valine methyl ester)·HCl resulted in 46% of the amide product.

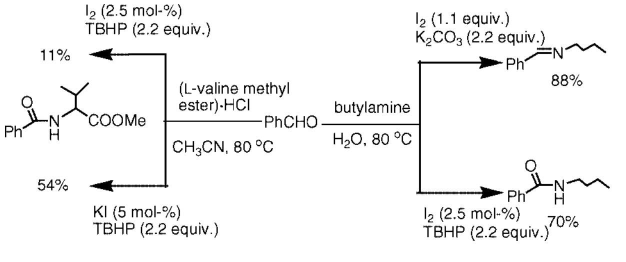
Table 3. KI-TBHP-catalyzed amidation of benzyl alcohols with primary amines.[a]



Entry	Aldehyde	Amide	Yield [%][b]
1			62
2			10
3			52
4			46[c] (>98% *ee*)

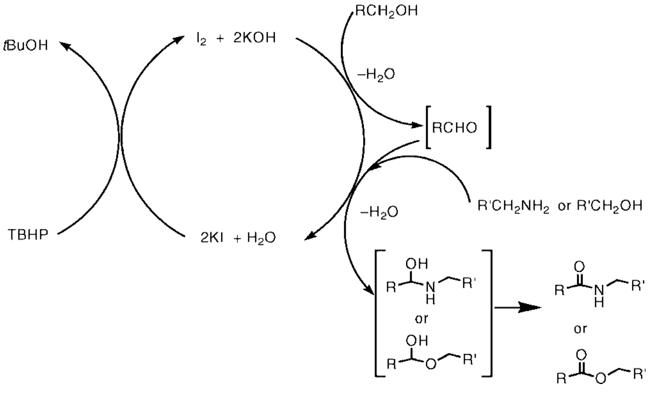
[a] Reaction conditions: alcohol (1 mmol), primary amine (1.2 mmol), TBHP (3.0 mmol), KI (0.20 mmol), H_2O (3 mL), 80 °C, 15 h. [b] Isolated yield. [c] 15% of aldehyde was observed.

Molecular iodine under alkaline conditions oxidizes alcohols and aldehydes to their corresponding esters via hemiacetal intermediates.[20,27] During our investigation on oxidative esterification of aldehydes with the KI-TBHP system, we observed that in situ generated iodine and KOH are the main catalytic species.[21] To probe the role of in situ generated iodine and KOH in the present oxidative amidation reactions, the following experiments shown in Scheme 2 were carried out. Reaction with iodine under alkaline conditions resulted only in the imine, whereas catalytic amounts of iodine and TBHP provided the amide product in 70% yield. These two experiments clearly prove that iodine and TBHP are necessary for amide formation. This is further confirmed by the reaction between benzaldehyde and butylamine with 2.5 mol-% of iodine and 2.2 mmol TBHP, which resulted in 70% of the amide product.[28] Similarly, the role of base is more pronounced in the oxidative amidation of aldehydes with amine hydrochloride salts. For example, the reaction between benzaldehyde and (L-valine methyl ester)·HCl in the presence of iodine and TBHP provided only 11% of the coupled product, whereas the same reaction in the presence of a combination of KI and TBHP provided 54% of the amide product. The latter result shows the role of the in situ generated base in activating the amine hydrochloride salt, which is similar to the observations made by Li and co-workers during the oxidative amidation of aldehydes with amine hydrochloride salts by using copper catalysts.[15]



Scheme 2. Confirmation of the role of iodine, TBHP, and base in oxidative amidation.

On the basis of the above results, we tentatively propose the mechanism as shown in Scheme 3. In the first step, TBHP oxidizes the potassium iodide to generate molecular iodine and potassium hydroxide. The reaction between aldehyde and primary amine may probably proceed via a hemiaminal intermediate, similar to the hemiacetal path in the case of oxidative esterification. In the case of direct amidation of benzyl alcohols, the reaction was expected to go through an aldehyde intermediate. Under the present conditions, it is believed that the iodide salt is re-oxidized to iodine by TBHP, which makes the reaction catalytic. The reaction between benzoic acid and butylamine under the present reaction conditions provided only 15% of the amide



Scheme 3. Proposed mechanism for the oxidative amidation of aldehydes with amines.

product, which rules out the alternative mechanism of in situ formation of carboxylic acids followed by a direct thermal amide formation.

Conclusions

We have developed a simple and straightforward method for the synthesis of the amide bond by oxidative coupling between an aldehyde/alcohol and an amine. In this strategy, no external base or additive is required. Moreover, the present methodology was extended to chiral amino acid derivatives, which are important intermediates in pharmaceuticals and synthetic organic chemistry. Formation of amides from alcohols, which is difficult to some extent, was also achieved in this preliminary study. The scope of this reaction is under investigation, and the results will be discussed in due course.

Experimental Section

General Procedure for the Synthesis of Amides from Amines: To a solution of aldehyde (1.0 mmol), potassium iodide (0.05 mmol), and amine (1.2 mmol) in water (3 mL) was added a solution of 70% aqueous TBHP (2.2 mmol) dropwise over a period of 30 min and while stirring at 80 °C. Progress of the reaction was monitored by TLC, and after completion of the reaction the mixture was quenched with saturated aqueous $Na_2S_2O_3$, washed with brine, extracted with ethyl acetate, and dried with anhydrous Na_2SO_4. Removal of the solvent under vacuum afforded the crude product, which was purified by column chromatography by using a hexane/ethyl acetate mixture and analyzed by ^1H NMR spectroscopy, gas chromatography, and GC–MS. A similar procedure was followed for the synthesis of amides from benzyl alcohol with primary amines.

Supporting Information (see footnote on the first page of this article): General information, experimental conditions, ^1H NMR and mass spectral data of all compounds.

Acknowledgments

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[28] Oxidative amidation of primary amines with catalytic amounts of iodine (2.5 mol-%) and TBHP for various aldehydes have provided the coupled product in good yield, and the results will be communicated in due course.

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