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Diacetoxyiodobenzene Mediated One-Pot Synthesis of Diverse Carboxamides from Aldehydes

Virendra Prasad, Raju R. Kale, Bhuwan B. Mishra, Dhananjay Kumar, and Vinod K. Tiwari*

Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi-5, India

Tiwari_chem@yahoo.co.in; vtiwari@ucdavis.edu

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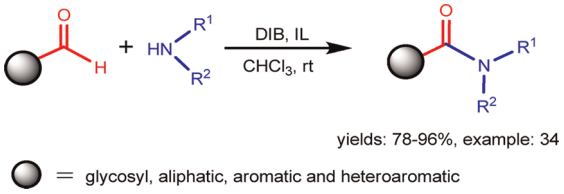
ABSTRACT



A novel, one-pot, and highly facile protocol has been devised for an easy access of a series of novel glycosyl carboxamides from aldehydes using diacetoxyiodobenzene in the presence of ionic liquid at ambient temperature.

The amide functionality is ubiquitous to a myriad of compounds of biological, pharmaceutical, agricultural, and material interests.[1] The most prevalent synthetic route to these nitrogen-containing compounds relies heavily upon the interconversion strategy between activated carboxylic acid derivatives and amine precursors.[2] However, instability of activated carboxylic acid derivatives restricts their pervasive applications and poses significant challenges.[3] Other methodologies to access amides include an azide based modified *Staudinger* reaction,[4] hydrative amide syntheses with alkynes,[5] thio acid/ester ligation methods,[6] and transition-metal-catalyzed carbonylations of alkenes,[7] alkynes,[8] and haloarenes with amines.[9] We have recently devised glycosyl carboxamides

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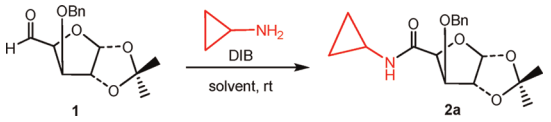
2 using a benzotriazole methodology, where glycosyl acylbenzotriazole obtained from **1** on treatment with various amines furnished **2** in good yields.[10] Despite the practical efficiency, the involvement of three steps and use of hazardous thionyl chloride limits the method in being explored in industry.

The most elegant atom economic approach for conversion of readily available aldehydes to amides apparently involves the direct reaction of an acyl C−H bond of aldehyde with amines in the presence of transition metals or other catalysts under oxidative conditions.[11] However, the lack of universality, use of expensive and toxic transition metals, modest to poor yields, harsh reaction conditions, and limited stability of the starting materials are the limitations that restrict their exploration and warrant searching for more general, efficient, and viable routes for amide bond synthesis. The conversion of diverse glycosyl uloses into corresponding amides under the mild conditions has not been realized so far. Thus, we envisioned exploring the feasibility of utilizing the oxidation potential of hypervalent iodine reagents[12] to access carboxamides of multifaceted biological profiles through a one-pot methodology from uloses.

At the outset of this study, we focused our attention on developing an oxidative amidation of glycosyl ulose through a one-pot procedure. Thus, glycosyl ulose **1** was reacted with cyclopropyl amine in anhydrous $CHCl_3$ at rt under catalysis of diacetoxyiodobenzene (DIB) to afford the **2a** in 50% yield. To assess the yield further, we performed the reaction of **3** with cyclopropyl amine and got **4a** in almost the same yield. We investigated the reaction intensively and observed that the concentration of amine decisively influenced the yield of the final product. A high concentration of amine was prone to oxidation and was readily oxidized by DIB when added promptly, thus resulting in a lower yield of the final compound. Therefore, the addition of amine was carried out dropwise with constant stirring and a nearly 2-fold increase in yield was observed.

We briefly studied the effect of solvents on the reaction time and yield. The results illustrated the poor performance of toluene, THF, DMF, DCE, and acetonitrile in terms of yield and reaction time. The reaction in methanol afforded a methyl ester of **1** along with **2a** obtained only in a trace amount. Dichloromethane performed well with respect to yield but required a slightly longer reaction time. The conversion of **1** into **2a** was eventually found to be facile only in $CHCl_3$ with good yield in a considerably shorter time, and hence $CHCl_3$ was established as the solvent of choice for the reaction (entry 8, Table 1). The molar ratios of the reactants were also found to have a profound effect on the outcome of the reaction. Toward this end, a series of reactions with different mole ratios of **1**, amines, and DIB were performed, and results suggested

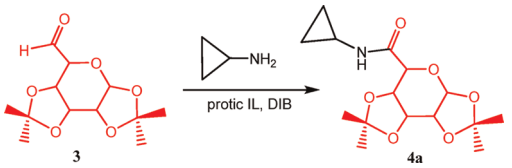
Table 1. Optimization of Oxidative Amidation of **1** with Cyclopropyl Amine in Various Solvents



entry	solvents	time[a] (h)	yield[b] (%)
1	DMF	30	34
2	THF	30	35
3	toluene	30	30
4	MeOH[c]	30	methyl ester
5	DCE	30	40
6	MeCN	30	40
7	CH_2Cl_2	30	45
8	$CHCl_3$	28	50

[a] Time required. [b] Isolated yields. [c] Complicated reaction.

Table 2. Optimization of Oxidative Amidation of **3** in the Presence of Different ILs on Model Reaction[a]



entry[a]	ionic liquids	solvent	time (h)	yield[b] (%)
1	$[MIM]^+[HSO_4]^-$	$CHCl_3$	23	85
2	$[MIM]^+[CH_3SO_3]^-$	$CHCl_3$	20	90
3	$[NMM]^+[HSO_4]^-$	$CHCl_3$	20	90
4	$[NMM]^+[CH_3SO_3]^-$	$CHCl_3$	18	90
5	$[BMIM]^+[BF_4]^-$	$CHCl_3$	18	92

[a] Glycosyl ulose **3** (1.0 mmol), DIB (1.5 mmol), cyclopropyl amine (1.5 mmol), and protic IL (catalytic amount). [b] Isolated yields.

the best molar ratio to be 1.0:1.5:1.5 for glycosyl ulose, amine, and DIB, respectively for optimum yields.

In recent years, room temperature ionic liquids (RTILs) capable of catalyzing the one-pot, multicomponent reactions of carbonyl compounds have emerged as promising environmentally benign reaction media in carbohydrate chemistry.[13] We next synthesized some ionic liquids[14] and evaluated their catalytic performance in the oxidative amidation of **3**, where the molar ratio of ILs to substrate was kept at less than 0.1. The results of oxidative amidation are outlined in Table 2, suggesting that all the ILs improved the yield significantly with a reduction in reaction time. However, $[BMIM]^+[BF_4]^-$ was the best suited catalyst for such a transformation. After screening various combinations of reagents, we arrived at a convenient

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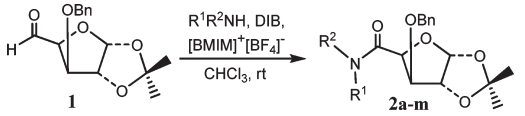
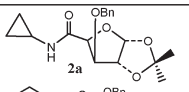
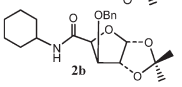
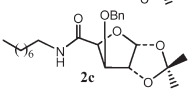
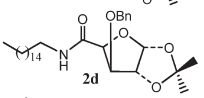
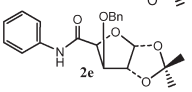
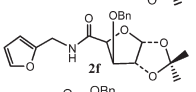
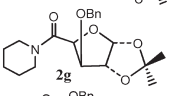
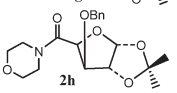
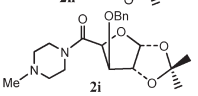
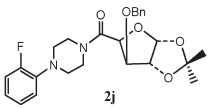
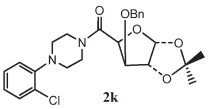
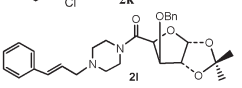
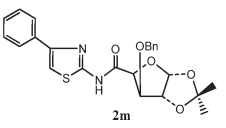
Table 3. Synthesis of Diverse Carboxamides from **1**

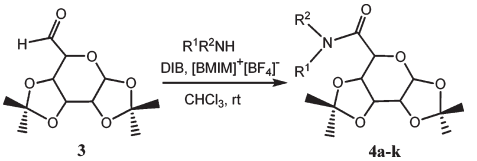


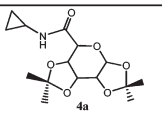
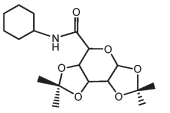
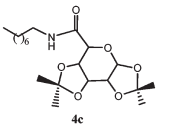
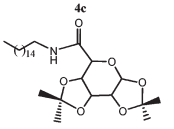
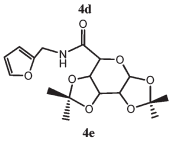
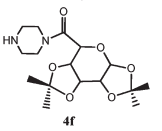
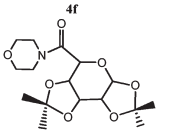
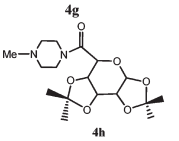
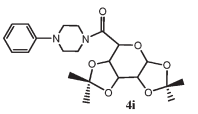
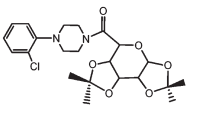
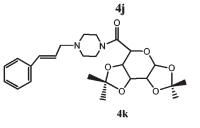
entry[a]	R^1R^2NH	product	yield[b] (%)
1	Cyclopropyl amine	 **2a**	90
2	Cyclohexyl amine	 **2b**	93
3	$CH_3(CH_2)_7NH_2$	 **2c**	92
4	$CH_3(CH_2)_{15}NH_2$	 **2d**	92
5	$C_6H_5NH_2$	 **2e**	80
6	Furfuryl amine	 **2f**	92
7	Piperidine	 **2g**	86
8	Morpholine	 **2h**	85
9	1-Methyl piperazine	 **2i**	85
10	1-(2-Fluro-phenyl)-piperazine	 **2j**	82
11	1-(2-Chloro-phenyl)-piperazine	 **2k**	84
12	1-(3-Phenyl-allyl)-piperazine	 **2l**	87
13	4-Phenyl-thiazol-2-yl-amine	 **2m**	82

[a] Molar ratios: glycosyl ulose, amine, DIB (1.0:1.5:1.5 mmol), and $[BMIM]^+[BF_4]^-$ (catalytic amount), reaction time 22 h. [b] Isolated yield.

procedure that performs well with **1** and **3** (1.0 mmol), cyclopropyl amine (1.5 mmol), and DIB (1.5 mmol) in the presence of a catalytic amount of $[BMIM]^+[BF_4]^-$ in $CHCl_3$. In order to explore the generality and scope of this process, a wide range of amines were studied to illustrate the efficacy of this novel and convenient method for the synthesis of diverse glycosyl carboxamides (Tables 3 and 4).

Table 4. Synthesis of Diverse Carboxamides from **3**

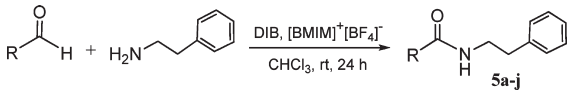


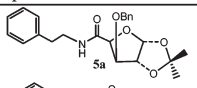
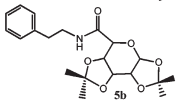
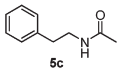
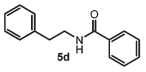
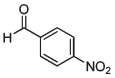
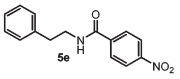
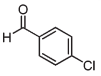
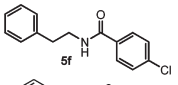
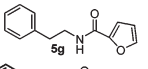
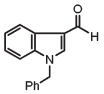
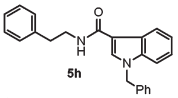
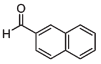
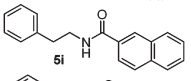
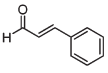
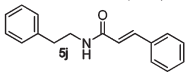
entry[a]	R^1R^2NH	product	yield[b] (%)
1	Cyclopropyl amine	 **4a**	92
2	Cyclohexyl amine	 **4b**	90
3	$CH_3(CH_2)_7NH_2$	 **4c**	90
4	$CH_3(CH_2)_{15}NH_2$	 **4d**	89
5	Furfuryl amine	 **4e**	80
6	Piperizine	 **4f**	84
7	Morpholine	 **4g**	82
8	1-Methyl piperazine	 **4h**	83
9	1-Phenyl piperazine	 **4i**	80
10	1-(2-Chloro-phenyl)-piperazine	 **4j**	78
11	1-(3-Phenyl-allyl)-piperazine	 **4k**	80

[a] Molar ratios: glycosyl ulose (1.0 mmol), DIB (1.5 mmol), amine (1.5 mmol), and $[BMIM]^+[BF_4]^-$ (in catalytic amount). [b] Isolated yield.

The oxidative amidation reactions of **1** with primary amines are relatively smoother than the secondary amines

Table 5. Synthesis of Diverse Carboxamides from Different Aldehydes



entry[a]	RCHO	product	yield[b] (%)
1	**1**		90
2	**3**		88
3			82[c]
4			90
5			96
6			92
7			86
8			78
9			90
10			88

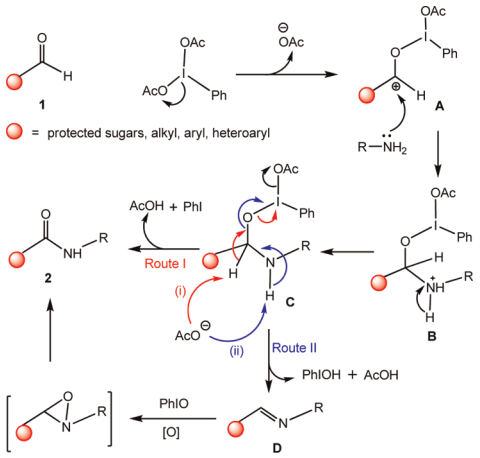
[a] Molar ratios: aldehyde, amine, DIB (1.0:1.5:1.5 mmol), and $[BMIM]^+[BF_4]^-$ (catalytic amount). [b] Isolated yield. [c] Reaction time 40 h.

(Table 3), delivering the products in higher yields. Similar trends were also observed in the case of the oxidative amidation of **3** (Table 4).

The methodology has been also successfully extended over a wide range of aliphatic, aromatic, and heteroaromatic aldehydes (Table 5). Like **1** and **3**, the aromatic and heteroaromatic aldehydes readily afforded corresponding carboxamides in good yields with similar reaction times (Table 5). Among the aromatic aldehydes, the presence of electron-withdrawing groups at the *p*-position resulted in a higher yield of corresponding products (**5f** and **5g**). However, the oxidative amidation of acetaldehyde required a longer reaction time (entry 3, Table 5) to afford the corresponding *N*-phenethylacetamide (**5c**) in 82% yield. Notably, this method is compatible with a number of functional groups such as halogen, nitro, and alkene giving their corresponding amides in good yield. The structures of all the novel carboxamides were deduced from their spectral studies (IR, ^1H, and ^{13}C NMR) and elemental analysis.

Although a detailed understanding of the mechanism for this amidation process will require additional studies, we

Scheme 1. Proposed Reaction Mechanism



assume that the transformation of glycosyl aldehyde **1** to glycosyl carboxamide **2** under the oxidation of DIB may proceed in two different pathways as outlined in Scheme 1. The oxidative transformation of **1** into amide **2** proceeds through intermediate **A**, which is formed in the first step by the nucleophilic attack of ulose **1** to DIB, as iodine in DIB acts as a good electrophilic center. Subsequently, amine attacks the electron-deficient carbonyl carbon leading to the formation of intermediate **B**, which after the loss of a proton affords intermediate **C**. Finally, the intermediate **C** may facilitate the formation of amide **2** in two different ways. The first possible path would involve the abstraction of the α-proton by the acetate ion leading to the amide, whereas the second route encompasses the formation of imine **D** which on oxidation,[11b] would fetch the oxaziridine and ultimately the target amide after cleavage of the N−O bond.

In conclusion, the DIB-catalyzed protocol described here provides a direct, simple, and efficient route to novel carboxamides from aldehydes and, thus, represents a formal oxidative amidation of aldehyde. This latest addition to the growing list of examples of the strikingly unique oxidation potential of DIB, to the best of our knowledge, is the first general method for a one-step oxidative amidation of aldehyde into amide under mild conditions using ionic liquids. As this chemistry eludes the use of expensive and toxic metals and tolerates the presence of functional groups, we feel that it may be recognized as an eco-friendly alternative to existing synthetic methods.

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Supporting Information Available. Experimental procedures and characterization of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.