A Mild and Clean Method for Oxidative Formation of Amides from Aldehydes and Amines

Chen Fang, Weixing Qian,* Weiliang Bao*

Department of Chemistry, Zhejiang University, Xi Xi Campus, Hangzhou, Zhejiang 310028, P. R. of China Fax +86(571)88273814; E-mail: wlbao@css.zju.edu.cn Received 16 April 2008

Abstract: A metal-free direct oxidative formation of amides from aldehydes and amines using a hypervalent iodine(III) reagent or an ion-supported hypervalent iodine(III) reagent as a recyclable oxidant under mild conditions is reported.

Key words: (diacetoxyiodo)benzene, ion-supported hypervalent iodine(III) reagent, direct oxidative formation of amides, amines, aldehydes

The amide group is a 'bio' functionality in view of its unique role in the peptides and is also a very important motif in pharmaceuticals, agricultural chemicals and natural products.¹ The treatment of activated derivatives of acids such as acyl halides, acid anhydrides or activated esters with ammonia or amines is the main route to obtain the primary, secondary and tertiary amides.² However, such activated carboxylic acid derivatives are usually unstable. Other preparative methods of amides such as Ritter reaction,³ solid-phase synthesis,⁴ tin-radical-catalyzed synthesis of α -methylene amides,⁵ hydrative amide synthesis with terminal alkyne and azide,⁶ and formation of amides from corresponding unactivated esters and lactones⁷ were also reported. These routes are problematic because of the limited or inconvenient procedures or poor atom economy. Direct oxidative formation of amides from aldehydes and amines was reported, but this method used expensive transition metal catalysts and exhibited poor substrate scope.⁸ Recently Li and co-workers developed a direct oxidative strategy by using tert-butyl hydroperoxide (TBHP) as an oxidant;⁹ however there are still some limitations. The amines must be converted to hydrochlorides to avoid oxidation and then liberated in situ by neutralization with inorganic base, and metal-containing catalyst, CuI–AgIO₃, was required. From both industrial and green chemistry points of view, the exploitation of efficient and environmentally benign methods for this transformation under mild reaction conditions is still demanded.

Recently, the impressive development of hypervalent iodine chemistry is prevalent. However, investigations on the reactivities of hypervalent iodine compounds and their efficient use as metal-free reagents in organic synthesis is still undergoing investigations.¹⁰ Among them, (diacet-

SYNLETT 2008, No. 16, pp 2529–2531 Advanced online publication: 22.08.2008 DOI: 10.1055/s-2008-1078218; Art ID: W06108ST © Georg Thieme Verlag Stuttgart · New York oxyiodo)benzene (DIB) is a popular one and has been extensively studied.¹¹ We have also been engaged in the research of the applications of DIB, although our main interest is the application of ion-supported hypervalent iodine compounds.¹² In our previous work, ion-supported hypervalent iodine compounds could efficiently oxidize alcohols¹² and thioethers.¹³ We found in the literature that DIB was a favorable oxidant for the formation of the C-N bond.¹⁴ We also noticed that the primary amines were not easily oxidized by DIB.¹⁵ Herein we were prompted to study the possibility of the direct oxidative formation of amides from aldehydes and amines oxidized by hypervalent DIB and its ion-supported analogue. Coincidently, Chan and co-workers investigated oxidative sulfamidation of aldehydes by using hypervalent iodine compounds as oxidants and rhodium(II) as catalyst.¹⁶

 Table 1
 Optimization of the Oxidative Amidation of Aldehydes

 with Amine in Different Solvents^a

CI	$H + H_2N$	DIB solvent, r.t.	O H H
1b	2b		3b
Entry	Solvent	Time (h)	Yield (%) ^b
1	THF- $H_2O(1:1)$	36	15
2	MeCN	36	17
3	DCE	36	24
4	CH_2Cl_2	36	38
5	CHCl ₃	36	42
6	CHCl ₃	20	40

^a Reaction conditions: 4-chlorobenzaldehyde (1.0 equiv), propan-1amine (1.0 equiv), DIB (1.1 equiv), solvent (1 mL).
^b Isolated yields based on 4-chlorobenzaldehyde.

Initially, DIB was utilized as the oxidant at room temperature. A brief optimization on the solvent effects revealed that the CHCl₃ and CH_2Cl_2 were good solvents. When CHCl₃ was used as the solvent, the reaction time could be reduced to 20 hours (Table 1). Traditionally, a metal catalyst was required in the oxidative amidation reaction. In our study, however, we observed the formation of **3b** in moderate yield without any metal catalyst when one equivalent of amine and one equivalent of DIB were used

Table 2 Oxidative Amidation of Aldehydes with Amine by DIB^a

О Н +	R'NH ₂	DIB O solvent, r.t. R	R'				
1a–I	2a,b	3a–n					
Entry	Aldehyde	R	Amine	R′	Time (h)	Product	Yield (%) ^b
1	1a	Ph	2a	<i>n</i> -Pr	20	3a	50
2	1b	$4-ClC_6H_4$	2a	<i>n</i> -Pr	20	3b	68
3	1c	$4-BrC_6H_4$	2a	<i>n</i> -Pr	20	3c	70
4	1d	$4-IC_6H_4$	2a	<i>n</i> -Pr	20	3d	75
5	1e	$2-ClC_6H_4$	2a	<i>n</i> -Pr	20	3e	46
6	1f	α -naphthalene	2a	<i>n</i> -Pr	20	3f	53
7	1g	$4-MeC_6H_4$	2a	<i>n</i> -Pr	20	3g	60
8	1h	4-MeOC ₆ H ₄	2a	<i>n</i> -Pr	20	3h	49
9	1i	3,4,5-(MeO) ₃ C ₆ H ₄	2a	<i>n</i> -Pr	20	3i	50
10	1j	$3-O_2NC_6H_4$	2a	<i>n</i> -Pr	36	3j	83
11	1k	$4-O_2NC_6H_4$	2a	<i>n</i> -Pr	36	3k	85
12	1j	$3-O_2NC_6H_4$	2b	Bn	36	31	58
13	1k	$4-O_2NC_6H_4$	2b	Bn	36	3m	55

^a Reaction conditions: benzaldehyde (1.0 equiv), amine (1.3 equiv), DIB (1.5 equiv), solvent(1 mL).¹⁷

^b Isolated yields based on benzaldehyde.

(entry 5). A copper catalyst such as CuI or CuBr was employed in the comparing reactions, but it did not show any catalytic activity.

In order to increase the yield, we slowly added the DIB into the mixture of aldehyde and amine, but the method did not work. Through observation, we suggested that the amine played an important role in determining the yield. The following two cases would affect the yields. One was that the amine at relatively high concentration was oxidized by DIB more readily. The other was that it condensed with aldehyde to form a Schiff base if the substrates were mixed at once. Therefore, the amine was slowly added into the reaction mixture in the presence of two drops of water in order to reduce the Schiff base formation. The molar ratio of aldehyde, amine and DIB was changed to 1.0:1.3:1.5. Indeed, the yield was significantly improved. Using these optimized conditions, we explored the scope of the oxidative amidation reaction of aldehydes **1a-k** with amines **2a,b** (Table 2). In terms of product yields, the presence of electron-withdrawing groups in the aromatic aldehyde was favorable for the formation of amides (Table 2, entries 2-4, 10, and 11), while electrondonating groups made nearly no difference to the formation of amides (entries 7–9). Reaction between sterically hindered aldehyde 1e and amine 2a resulted in a lower yield (Table 2, entry 5). When aliphatic aldehydes and amines were mixed together, several products could be identified by TLC.

As ion-supported hypervalent DIB ([dibmim]⁺[BF₄]⁻) possesses the advantage of easy recovery and reuse, we studied the effect of 1-(4-diacetoxyiodobenzyl)-3-meth-ylimidazolium tetrafluoroborate ([dibmim]⁺[BF₄]⁻) in the direct oxidative amidation reaction. Because [dibmim]⁺[BF₄]⁻ was nearly insoluble in CHCl₃, a solvent mixture of CHCl₃ and MeCN (1:1) was used instead. The yields of the reaction in the presence of [dibmim]⁺[BF₄]⁻ were slightly lower than those from using DIB under the same reaction (Table 3). Notably, this oxidant showed its unique recyclable feature. By evaporating the reaction solvents and adding diethyl ether which was almost immiscible with [dibmim]⁺[BF₄]⁻, the products could be directly extracted from the reaction mixture and the oxidant could be easily recovered and recycled.¹⁸

With regard to the reaction mechanism, one possible pathway, as proposed by Wang and co-worker, would involve an oxidation of the imine to an oxaziridine, which would in turn result in the cleavage of the N–O bond to form the target amide.¹⁹ We then tried to oxidize (4-chlorobenzylidene)propanimine by DIB, and 35% of the desired amide was formed after 20 hours. The other possible pathway would be that nucleophilic addition of the amine to aldehyde would generate a carbinolamine intermediate, which would get oxidized into the desired amide products by the hypervalent iodine(III) reagent or ion-supported hypervalent iodine(III) reagent. Table 3 Oxidative Amidation of Aldehydes with Amine by [dib-mim]⁺ $[BF_4]^-$



^a Reaction conditions: benzaldehyde (1.0 equiv), amine (1.3 equiv), [dibmim]⁺ $[BF_4]^-$ (2.0 equiv), solvent (1 mL).

^b Isolated yields based on benzaldehyde.

In summary, we have developed a mild and efficient oxidant for the formation of amides from aldehydes and amines. The easy availability of the starting materials, the simplicity and the high efficiency of the reaction procedure, the recoverable and recyclable properties of the oxidants, as well as the mild reaction conditions should render this protocol attractive to synthetic chemists.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

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- (17) All reagents and solvents were pure analytical grade materials purchased from commercial sources and were used without further purification, if not stated otherwise. All melting points are uncorrected. The NMR spectra were recorded in CDCl₃ on a Bruker Avance 400 MHz instrument with TMS as internal standard. TLC was carried out with 0.2 mm thick silica gel plates (GF254). The columns were hand packed with silica gel 60 (200-300 µm). All products were confirmed by ¹H NMR and ¹³C NMR. Unknown compounds were additionally confirmed by elemental analysis. Typical Procedure for the Oxidative Amidation of Aldehydes with Amines by DIB: A solution of aldehyde (0.50 mmol, 1.0 equiv), DIB (0.75 mmol, 1.5 equiv), and two drops of H₂O in CHCl₃ (1 mL) was cooled to 0 °C under an inert atmosphere (N_2) and the amine (0.65 mmol, 1.3 equiv) was slowly added (about one drop in 1 h for 3 h). The reaction vessel was capped and the reaction mixture was stirred for 3 h at 0 °C and then for 17 h at r.t. The crude reaction mixture was purified by column chromatography on silica gel (EtOAc-hexane, 1:4).

3,4,5-Trimethoxy-*N***-propylbenzamide (Table 2, entry 9)**: white solid; mp 108 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.00 (s, 2 H), 6.25 (br, 1 H), 3.89 (s, 6 H), 3.87 (s, 3 H), 3.40 (q, *J* = 6.8 Hz, 2 H), 1.60–1.69 (m, 2 H), 0.98 (t, *J* = 8.0 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 167.3, 153.1, 140.7, 130.3, 104.3, 60.8, 56.2, 41.8, 22.9, 11.4. Anal. Calcd for C₁₃H₁₉NO₄: C, 61.64; H, 7.56; N, 5.53; O, 25.27. Found: C, 61.60; H, 7.65; N, 5.60.

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