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ARTICLE TYPE

Iodide-catalyzed Amide Synthesis from Alcohols and Amines

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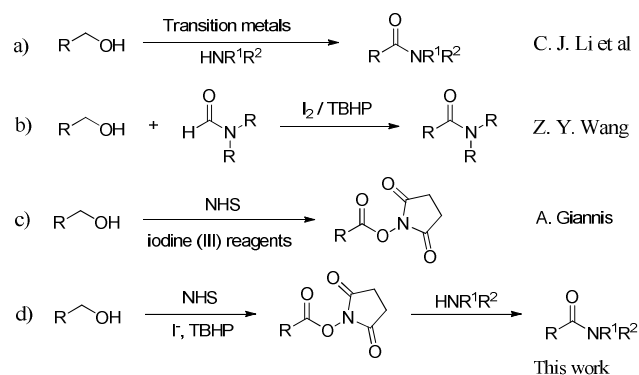
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5 An efficient method to prepare amides by a cascade strategy was developed. Using *n*Bu₄NI or NaI as the catalyst and *tert*-butyl hydroperoxide as the oxidant, various alcohols reacted with N-hydroxysuccinimide or N-hydroxyphthalimide affording corresponding active esters in moderate to good yield. The resulted active esters were converted into amides smoothly in one pot.

Introduction

10 Amide bond is one of the most abundant units in a wide range of natural products, polymers, agrochemicals, and pharmaceuticals with biologically relevant properties.¹ The synthesis of amides has therefore attracted considerable interest and a number of methods have been devised. They are routinely prepared from the
15 acylation of amines with activated carboxylic acids, especially with N-hydroxyimide esters.² Oxidative amidation of alcohols or aldehydes are economically attractive alternatives to traditional synthesis. Research during the past decade resulted in significant progress in the field of amidation of aldehydes.^{3,4} Considering the
20 stability and the availability of alcohols, chemists have been focusing on the direct conversion of alcohols and amines into amides, which is more atom-economical and environmentally benign. In spite of great progresses, the use of transition-metal catalysts⁵ or the need for more than stoichiometric amounts of
25 hypervalent iodine (III) reagents⁶ limits the practical application of this strategy.



Scheme 1. Methods to amidation of alcohols

30 Wang et al developed an amide formation reaction of alcohol with N,N-disubstituted formamides leading to N,N-disubstituted amides without the use of a hypervalent iodine (III) reagent or a metal catalyst.⁷ However, nitrogen source is limited to pre-
35 formed formamides. Quite recently, Yamamoto et al reported the

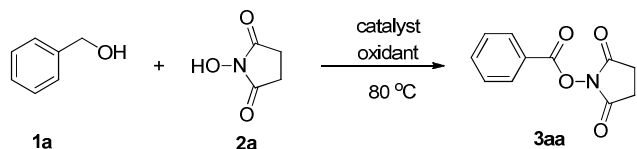
first metal-catalyzed amidation reaction of aldehyde using N-hydroxyimide as a dual promoter of aldehyde oxidation and amines displacement.⁸ Barbas III groups reported the first organocatalytic amidation reaction of aldehyde using the same
40 strategy.⁹ We envisioned that an iodide reagent also could catalyze the oxidation of alcohols into N-hydroxyimide esters, which facilitate the displacement of an amine. This tandem strategy will alleviate structural dependence on amines.

Results and discussion

45 Our initial studies focused on the model reaction of phenylmethanol **1a** with N-hydroxysuccinimide (NHS) **2a** in acetonitrile. Without a catalyst, no desired product was observed.

Table 1. Optimization of the reaction conditions^a

50



Entry	Catalyst	Oxidant	Yield
1	-	aqueous TBHP	N.D.
2	NaI	aqueous TBHP	71%
3	<i>n</i> Bu ₄ NI	aqueous TBHP	82%
4	I ₂	aqueous TBHP	N.D.
5	PhI(OAc) ₂	aqueous TBHP	N.D.
6	<i>n</i>Bu₄NI	anhydrous TBHP	85%
7	<i>n</i> Bu ₄ NI	DTBP	N.D.
8	<i>n</i> Bu ₄ NI	H ₂ O ₂	N.D.
9 ^b	<i>n</i> Bu ₄ NI	anhydrous TBHP	80%
10 ^c	<i>n</i> Bu ₄ NI	anhydrous TBHP	76%

^a **1a** (0.5 mmol), NHS (0.75 mmol), catalyst (10 mol %), oxidant (4.0 equiv) in acetonitrile (2 mL) at 80 °C for 18 hours. ^b Ethyl acetate as the solvent. ^c Using 0.5 mmol of NHS. H₂O₂: 50% hydrogen peroxide in water; DTBP: di-*tert*-butyl-peroxide.

With NaI as the catalyst and aqueous *tert*-butyl hydroperoxide (TBHP 70 wt.% in water) as the oxidant, the desired active ester

3aa was isolated in 71% yield (Table 1, entry 2). We further found *n*Bu₄NI was more effective than NaI (Entry 3 vs entry 2) and iodine or PhI(OAc)₂ was inactive.

Replacement of the aqueous TBHP with anhydrous TBHP (5.5 M in decane) led to a slightly increased yield (Entry 6 vs entry 3). Other oxidants like H₂O₂ or DTBP did not work for this transformation (Entries 7, 8). Using ethyl acetate instead of acetonitrile as the solvent, this reaction gave **3aa** in slightly decreased yield (Entry 9). Other solvents including toluene, tetrahydrofuran, ethanol and 1,4-dioxane were not suitable for this reaction. Reducing the amount of NHS resulted in an obvious decreased yield (Entry 10 vs entry 6).

With the optimized conditions in hand, the substrate scope of the reaction was investigated. Benzyl alcohols with electron-

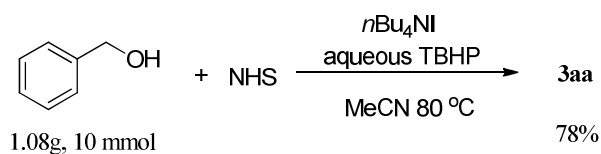
15 donating or weak electron-withdrawing groups were well tolerated and provided the corresponding esters in high yields (Table 2). *Ortho*-substituted benzyl alcohols (**1h** and **1i**) also provided the products in good yields. Electron effects influence the reaction. Strong electron-withdrawing substituents retarded this reaction obviously. For example, when 4-cyano benzyl alcohol was coupled with NHS, low yield of **3ka** was obtained. The aromatic rings of the reaction substrates could also be naphthyl, thienyl, and furyl rings (**1j**, **1l** and **1m**). Using aqueous TBHP as the oxidant, most benzyl alcohols gave esters in 25 decreased but acceptable yields. Insufficiently, alkyl alcohols didn't undergo such transformation, suggesting that an aromatic functionality is necessary to stabilize the active species.

Table 2. Oxidative esterification of alcohols with NHS ^a

Alcohol	Product	Yield (%)	Alcohol	Product	Yield (%)
	1a 3aa	85 82 ^b		1h 3ha	85
	1b 3ba	83 86 ^b		1i 3ia	73
	1c 3ca	90		1j 3ja	84
	1d 3da	83 76 ^b		1k 3ka	26
	1e 3ea	92 64 ^b		1l 3la	53
	1f 3fa	81 57 ^b		1m 3ma	35
	1g 3ga	77		1n 3na	30

^a Standard conditions: alcohol (0.5 mmol), NHS (0.75 mmol), *n*Bu₄NI (10 mol %), anhydrous TBHP (4.0 equiv), acetonitrile (2 mL), 80 °C, 18 hours. ^b Using aqueous TBHP (4.0 equiv) as the oxidant.

In support of the utility of this method, we conducted this reaction on a gram scale using aqueous TBHP as the oxidant. As shown in scheme 2, the product was obtained with good yield.



Scheme 2. Preparative scale experiment.

Unexpectedly, when the reaction was carried out with N-hydroxyphthalimide (NHPI) **2b**, under the above conditions only 67% of **3ab** was isolated. After screening catalysts, bases and solvents (see table S1 in the support information), we found NaI was a good catalyst and a strong base was a good promoter. The optimal reaction conditions were determined to be: 10 mol % of NaI (catalyst), 0.4 equiv of KOH (base), 4 equiv of aqueous TBHP (oxidant), 2 mL of ethyl acetate (solvent), reaction temperature at 80°C under air atmosphere for 8 h.

Employing the above experimental conditions, a series of aromatic primary alcohols were efficiently oxidized to the corresponding active esters. As shown in table 3, most benzyl alcohols with electron-donating or weak electron-withdrawing substituents provided NHPI esters in good yields. Steric effects influence this reaction obviously. For example, naphthalenylmethanol and *ortho*-chlorophenylmethanol provided the desired product in low yield.

Table 3. Oxidative esterification of alcohols with NHPI^a

Alcohol	Product	Yield (%)	Alcohol	Product	Yield (%)
	3ab	93		3hb	77
	3bb	90		3ib	44
	3db	88		3jb	44
	3eb	89		3lb	92
	3fb	74		3mb	47

^a Conditions: alcohols (0.5 mmol), NHPI (0.75 mmol), NaI (10 mol %), KOH (0.4 eq), aqueous TBHP (4.0 equiv), ethyl acetate (2 mL), 80 °C, 8 hours.

Next, we examined the amine displacement step (Table 4). Treatment of the isolated NHPI ester **3ab** with benzylamine provided the expected amide **4a** in moderate yield. In contrast, NHS ester **3aa** provide the desired amide **4a** in high yield, suggesting NHS ester is more reactive for the displacement of an amine.

Table 4. Examination of the amine displacement.

Ester	Product	Yield (%)
3aa	4a	95
3ab	4a	62

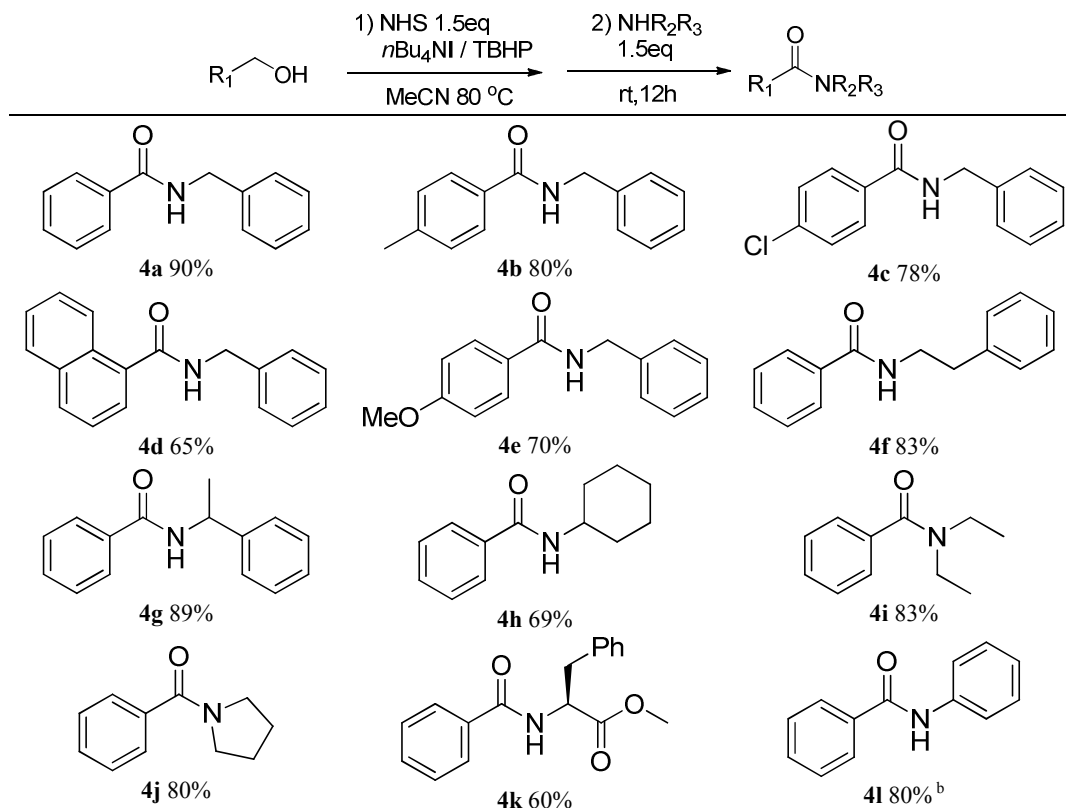
To further demonstrate its practical utility, we investigated the feasibility of a one-pot transformation of alcohols into amides. When amines were added to the resulted mixtures, we discovered

that the desired amide products were readily obtained in good yields (Table 5). This one-pot amidation of alcohols can be applicable to primary amines, secondary amines and even arylamines.

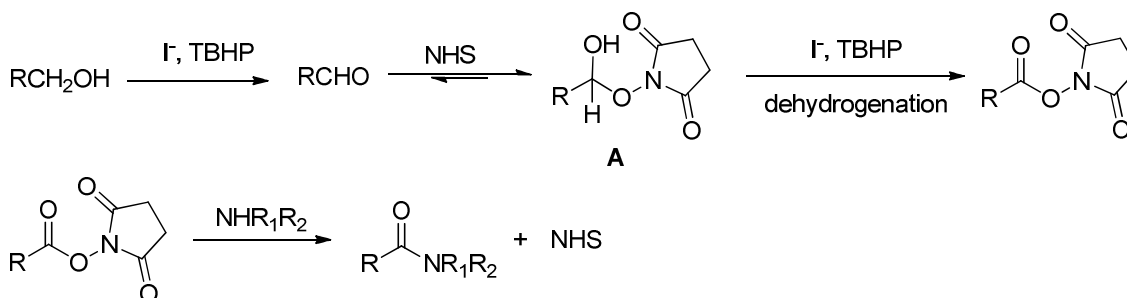
In terms of the previous reports,^{7,9} a proposed mechanism is shown in scheme 3. Alcohols are oxidized into aldehydes under I⁺/TBHP system. Then N-hydroxyimide attacks aldehydes to generate acetal A, which can be further oxidized to the product esters. Last, active esters convert into amides smoothly in the presence of amines.

Conclusions

In conclusion, an efficient one-pot oxidative amide synthesis from benzyl alcohols and amines was developed. Using iodide as the catalyst could avoid the use of stoichiometric amounts of hypervalent iodine (III) reagents, thus reducing the resulted by-products. This metal-free protocol provides a practical synthetic tool for the construction of amides from benzyl alcohols.

Table 5. One pot synthesis of amides^a

^a Conditions: (1) alcohol (0.5 mmol), NHS (0.75 mmol), CH₃CN (2 mL), *n*Bu₄NI (0.05 mmol) and anhydrous TBHP (4.0 equiv) 80 °C for 18h. (2) amine (0.75 mmol) at room temperature for 12 h. ^b The second step was performed at 50 °C.

**Scheme 3.** A proposed mechanism for synthesis of amides

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A metal free procedure for the synthesis of amides from benzyl alcohols and various amines is described.

