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ARTICLE TYPE

Et$_4$NI-Catalyzed Amidation of Aldehydes and Alcohols with Ammonium Salts

Gao Wang,[a] **Qing-Ying Yu,**[a] **Shan-Yong Chen*[a] and Xiao-Qi Yu *[a]**

An efficient method for the oxidative amidation of benzylic aldehydes or alcohols with ammonium salts has been developed for the synthesis of primary amides using Et$_4$NI as the catalyst and tert-butyl hydroperoxide as the oxidant. This amidation reaction is operationally straightforward and provides primary amides in moderate to good yields under mild conditions.

10 Introduction

The amide formation reaction is one of the key cornerstone reactions in modern chemistry and biology.[1] A traditional procedure for amide synthesis is the union of carboxylic acids and derivatives (acyl halides, anhydrides, or esters) with amines,
15 including ammonia. Although they are remarkably general, these methods present several drawbacks, such as the use of toxic, corrosive, and/or expensive materials, highly exothermic reactions, low tolerance to sensitive functional groups, complex reaction conditions, and wasteful procedures.[2]
20 The oxidative amidation of amines with aldehydes or alcohols is an economically attractive alternative to traditional methods, and many reactions based on this strategy have been developed.[3] However, the direct oxidative amidation of ammonia with aldehydes or alcohols is difficult because catalysts are deactivated
25 in the presence of ammonia and/or dehydration rather than dehydrogenation of the hemiaminal readily occurs.[4, 5a] Mizuno and Xiao groups developed an efficient method for the synthesis of primary amides from alcohols and ammonia in the presence of manganese oxide at high temperatures (Scheme 1, equation a).[5]
30 However, an excess amount of OMS-2 (manganese oxide octahedral molecular sieves, ca. 2 equiv.) was still required. Recently, Chen *et al.* reported a practical method for the amidation of aldehydes with ammonium chloride for the synthesis of primary amides using Cu$_2$O as the catalyst and
35 TBHP as the oxidant (Scheme 1, equation b). [6] However, the yields of this reaction are moderate. The metal-free synthesis of primary amides via the hydration of in situ-generated nitriles was also developed (Scheme 1, equation c).[7] However, an equivalent amount of iodine and a significant excess of ammonia and
40 oxidant were used. Furthermore, explosive triiodide monoamine may be produced in this system. Therefore, the development of new environmentally friendly procedures is still in demand.

Recently, iodide catalysts were found to be highly effective to replace the transition-metal catalysts in some coupling reactions,
45 which is as well according to the view of green chemistry.[8, 9] Lately, our group also reported that some *n*Bu$_4$NI catalyzed

amidation and esterification by using TBHP as an oxidant.[10] Herein, we developed an efficient procedure for the synthesis of primary amides via iodide-catalyzed direct amidation of
50 aldehydes or alcohols with ammonium.
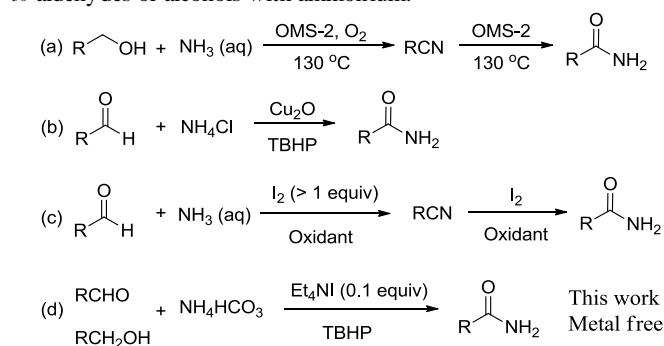
Scheme 1. Amidation reactions of aldehydes or alcohols with ammonia/ ammonium

Results and discussion

55 Our initial studies focused on the model reaction of benzaldehyde with aqueous ammonia (28%). With NaI as the catalyst and TBHP as the oxidant, the desired benzamide was isolated in 58% yield. Undesirable benzoic acid and benzonitrile were also obtained (Scheme 2). A range of ammonium salts were applied
60 to this transformation. Inexpensive ammonium bicarbonate (NH$_4$HCO$_3$) was a good ammonia donor (Table 1, entry 5 vs. entries 1-4). Among the catalysts screened, tetraethylammonium iodide (Et$_4$NI) gave the best yield (Entries 7-11). Only a trace amount of the product was detected in the absence of a catalyst or
65 an oxidant. The influence of the solvent was also studied. When other solvents, such asacetonitrile, fluorobenzene, ethyl acetate and H$_2$O were applied instead of 1, 2-dichloroethane (DCE), the desired product was also obtained with a slightly decreased yield (Entries 12-15). The optimal reaction conditions were Et$_4$NI (10
70 mol %), ammonium bicarbonate (3 equiv) and TBHP (3equiv) with DCE as the solvent.
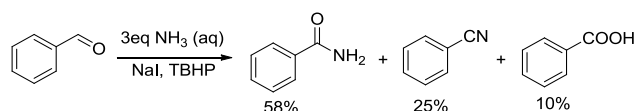
Scheme 2. Amidation reactions of aldehydes

Table 1. Optimization of the reaction conditions [a]

Entry	Catalyst	Ammonium	Solvent	Yield[b] (%)
1	NaI	NH$_3$(aq)	DCE	58
2	NaI	NH$_4$F	DCE	60
3	NaI	NH$_4$Cl	DCE	trace
4	NaI	(NH$_4$)$_2$HPO$_4$	DCE	40
5	NaI	NH$_4$HCO$_3$	DCE	66
6	-	NH$_4$HCO$_3$	DCE	trace
7	Et$_4$NI	NH$_4$HCO$_3$	DCE	83
8	I$_2$	NH$_4$HCO$_3$	DCE	55
9	nBu$_4$NI	NH$_4$HCO$_3$	DCE	77
10	nBu$_4$NBr	NH$_4$HCO$_3$	DCE	49
11	PhI(OAc)$_2$	NH$_4$HCO$_3$	DCE	trace
12	Et$_4$NI	NH$_4$HCO$_3$	MeCN	64
13	Et$_4$NI	NH$_4$HCO$_3$	H$_2$O	67
14	Et$_4$NI	NH$_4$HCO$_3$	Fluorobenzene	80
15	Et$_4$NI	NH$_4$HCO$_3$	Ethyl acetate	67

[a] Reactions was carried out with benzaldehyde (0.5 mmol), ammonia water (28%) or inorganic ammonium salt (3eq), catalyst (10 mol %) and TBHP (3.0 equiv) in the chosen solvent (2 mL) at 70 ℃, 22 h. [b] Yield is based on benzaldehyde.

With the optimized conditions in hand, the substrate scope of the reaction was investigated. A broad range of primary amides was successfully prepared using this protocol. Generally, benzaldehydes with electron-donating or weak electron-withdrawing groups produced the corresponding amides in good yields (Table 2). The reaction is sensitive to electronic effects and steric effects. Strong electron-withdrawing substituents obviously retarded this reaction. For example, when 4-nitrobenzaldehyde was applied to this transformation, a significantly depressed yield of **3k** was obtained. Five-membered heteroaryl aldehydes yielded the products with moderate to good yields (Compounds **3n**-**3q**). Interestingly, 5-bromothiophene-2-carbaldehyde performed more efficiently than other five-membered heterocylics. Alkyl aldehydes also underwent such a transformation, albeit with low yield (Table 2, **3r**). In support of the utility of this method, we conducted this reaction on a gram scale, and product **3a** was obtained with a 71% yield (Table 2, entry 2).

Table 2. Amidation of aldehydes [a]

Entry	Aldehyde	R`	Product	Yield (%)
1		**H**	**3a**	83
2		**H**	**3a**	71[b]
3		**4-Me**	**3b**	79
4		**2-Me**	**3c**	72
5		**4-F**	**3d**	83
6		**4-Cl**	**3e**	80
7		**3-Cl**	**3f**	45
8		**2-Cl**	**3g**	26
9		**4-Br**	**3h**	77
10		**4-CF$_3$**	**3i**	49
11		**4-MeO**	**3j**	72
12		**4-NO$_2$**	**3k**	35
13			**3l**	67
14			**3m**	39
15			**3n**	56
16			**3o**	76[c]
17			**3p**	56[c]
18			**3q**	90[c]
19	n-C$_7$H$_{15}$CHO		**3r**	32

[a] Reaction was carried out with aldehyde (0.5 mmol), NH$_4$HCO$_3$ (3eq), Et$_4$NI (10 mol %), and TBHP (3.0 equiv) in DCE (2 mL) at 70 ℃ for 22 h. [b] benzaldehyde (10 mmol). [c] Using MeCN (2 mL) as the solvent.

Considering the stability of alcohols, the direct conversion of alcohols with ammonium to produce primary amidesis is more attractive. Much to our satisfaction, the cascade amidation proceeded smoothly with different benzylic alcohols to produce a wide range of corresponding primary amides under similar conditions with moderate to good yields (Table 3).[11] However, using alkyl alcohols as the substrates led to low yield (Table 3, 12).

Table 3. Amidation of primary alcohols [a]

| Entry	Alcohol	R`	Yield (%) -CONH$_2$	Yield (%) -CN
1		**H**	89	<5
2		**4-Me**	76	15
3		**2-Me**	69	<5
4		**4-F**	77	<5
5		**4-Cl**	82	<5
6		**3-Cl**	45	12
7		**2-Cl**	43	10
8		**4-Br**	62	30
9		**4-MeO**	52	35
10			45	50
11			34[b]	63
12	n-C$_7$H$_{15}$CH$_2$OH		20	<5

[a] Reaction was carried out with alcohols (0.5 mmol), NH$_4$HCO$_3$ (3eq), Et$_4$NI (10 mol %) and TBHP (4.0 equiv) in DCE (2 mL) at 70 ℃ for 22 h. [b] Using MeCN (2mL) as the solvent.

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Interestingly, iodide could also realize the oxidative amidation of methyl ketones. For example, the oxidative amidation reaction of acetophenone **4a** with ammonium iodide provided primary ketoamide **5a** in 40% yield (Scheme 3). To the best of our knowledge, the oxidative coupling reaction of methyl ketones with ammonium salts/ammonia leading to α-ketoamides has not been reported.[12]
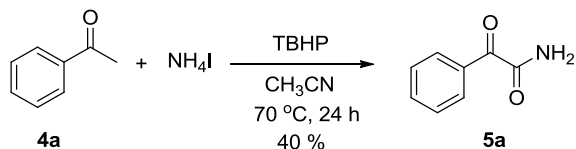

Scheme 3. Oxidative amidation of acetophenone

To gain insight into the mechanism of the reaction, some control experiments were set up. When benzonitrile was used rather than aldehydes or alcohols, no obvious amide formation was observed (Scheme 4, equation 1). Therefore, this transformation does not proceed through a nitrile intermediate as has been reported in the iodine or manganese oxide-promoted systems.[5, 7] When 20 mol % 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, a radical scavenger) was added to the reaction mixture, the amidation process was significantly inhibited (Scheme 4, equation 2). In terms of these experimental results and the previous reports,[3, 13] a proposed mechanism is shown in scheme 5. Alcohols are oxidized into aldehydes under the Et$_4$NI/TBHP system. Then, ammonia attacks aldehydes to generate hemiaminal A, which can then be converted into amides via dehydrogenation.
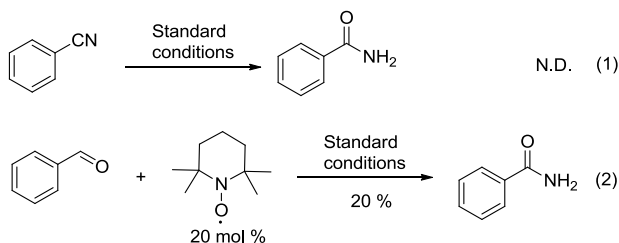
Scheme 4. Control experiments
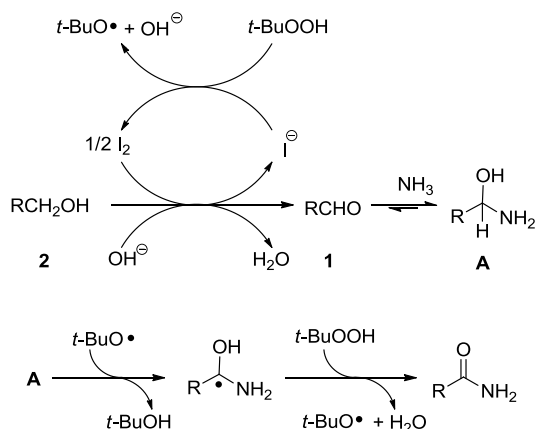
Scheme 5. A proposed mechanism

Conclusions

In summary, we have developed an efficient Et$_4$NI-catalyzed protocol for the formation of primary amides from benzylic

aldehydes or alcohols with ammonium. The straightforward process described here is simple, highly effective, and makes use of readily available starting materials, all of which should render this method attractive for synthesizing primary amides.

Notes and references

[a] *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China.*
Tel.: (86)-28-85415886; fax: (86)-28-85415886; E-mail: chensy@scu.edu.cn; xqyu@scu.edu.cn

1   (a) M. J. Humphrey, R. A. Chamberlin, *Chem. Rev.* 1997, **97**, 2243; (b) T. Cupido, J. Tulla-Puche, J. Spengler, F. Albericio, *Curr. Opin. Drug Discovery Dev.* 2007, **10**, 768; (c) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* 2011, **40**, 3405; (d) V. R. Pattabiraman, J. W. Bode, *Nature* 2012, **480**, 471; (e) R. M. Wilson, J. L. Stock-dill, X. Wu, X. Li, P. A. Vadola, P. K. Park, P. Wang, S. J. Danishef-sky, *Angew. Chem.* 2012, **124**, 2888; *Angew. Chem. Int. Ed.* 2012, **51**, 2834.

2   (a) D. Dopp, H. Dopp, Eds. *Methoden der Organischen Chemie (Houben Weyl)*; Thieme: Stuttgart, 1985; Vol. E5 (2), 1024-1031; (b) P. D. Bailey, T. J. Mills, R. Pettecrew, R. A. Price, *Comprehensive Organic Functional Group Transformations II*, 2005, **5**, 201-294; (c) E. Valeur, M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606.

3   (a) K. R. Reddy, C. U. Maheswari, M. Venkateshwar and M. L. Kantam, *Eur. J. Org. Chem.* 2008, **21**, 3619; (b) K. Ekoue-Kovi, C. Wolf, *Chem. Eur. J.* 2008, **14**, 6302; (c) A. J. A. Watson, J. M. J. Williams, *Science* 2010, **329**, 635; (d) C. Chen, S. H. Hong, *Org. Biomol. Chem.* 2011, **9**, 20; (e) J.-F. Soule, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* 2011, **133**, 18550.

4   (a) K. Nakagawa, H. Onoue, K. Minami, *Chem. Commun. (London)* 1966, 17-18; (b) C. Gunanathan, Y. Ben-David, D. Milstein, *Science*, 2007, **317**, 790; (c) A. J. A. Watson, A. C. Maxwell, J. M. J. Williams, *Org. Lett.* 2009, **11**, 2667.

5   (a) K. Yamaguchi, H. Hobayashi, T. Oishi, N. Mizuno, *Angew. Chem. Int. Ed.* 2012, **51**, 544; (b) R. Nie,; J. Shi, S. Xia, L. Shen, P. Chen, Z. Hou, F.-S. Xiao, *J. Mater. Chem.* 2012, **22**, 18115.

6   S. C. Ghosh, J. S. Y. Ngiam, A. M. Seayad, D. T. Tuan, C. L. L. Chai, A. Chen, *J. Org. Chem.* 2012, **77**, 8007.

7   (a) J.-J. Shie, J.-M. Fang, *J. Org. Chem.* 2003, **68**, 1158; (b) R. Ohmura, M. Takahata, H. Togo, *Tetrahedron Lett.* 2010, **51**, 4378.

8   For the recent reports on tetra-alkylammonium iodide catalytic reactions, see: (a) M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, *Science* 2010, **328**, 1376; (b) M. Uyanik, D. Suzuki, T. Yasui, K. Ishihara, *Angew. Chem., Int. Ed.* 2011, **50**, 5331; (c) T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner, B. J. Nachtsheim, *Org. Lett.* 2011, **13**, 3754; (d) M. Lamani, K. R. Prabhu, *J. Org. Chem.* 2011, **76**, 9552; (e) L.-T. Li, J. Huang, H. -Y. Li, L.-J. Wen, P. Wang, B. Wang, *Chem. Commun.* 2012, **48**, 5187; (f) M. Uyanik, K. Ishihara, *ChemCatChem* 2012, **4**, 177; (j) J. A. Souto, D. Zian, K. Muñiz, *J. Am. Chem. Soc.* 2012, **134**, 7242; (h) E. Shi, Y. Shao, S. Chen, H. Y. Hu, Z. J. Liu, J. Zhang, X. B. Wan, X. B. *Org. Lett.* 2012, **14**, 2936. (i) J. Xie, H. L. Jiang, Y. X. Cheng, C. J. Zhu, *Chem. Commun.* 2012, **48**, 979; (j) Q. C. Xue, J. Xie, H. M. Li, Y. X. Cheng, C. J. Zhu, *Chem. Commun.* 2013, **49**, 3700.

9   For the recent reports on iodide catalytic amidation, see: (a) Y. Wang, D. Zhu, L. Tang, S. Wang, Z. Wang, *Angew. Chem. Int. Ed.* 2011, **50**, 8917; (b) Z. J. Liu, J. Zhang, S. L. Chen, E. Shi, Y. Xu, X. B. Wan, *Angew. Chem. Int. Ed.* 2012, **51**, 3231; (c) J.-S. Tian, K. Wai, J. Ng, J.-R. Wong, T.-P. Loh, *Angew. Chem. Int. Ed.* 2012, **51**,

9105; (d) B. Tan, N. Toda, C. F. Barbas III, *Angew. Chem. Int. Ed.* 2012, **51**, 12538; (e) K. Xu, Y. Hu, S. Zhang, Z. Zha, Z. Wang, *Chem. Eur. J.* 2012, **18**, 9793; (f) H. M. Li, J. Xie, Q. C. Xue, Y. X. Cheng, C. G. Zhu, *Tetrahedron Let.* 2012, **53**, 6479; (g) W.-P. Mai, G. Song, J.-W. Yuan, L.-R. Yang, G.-C. Sun, Y.-M. Xiao, P. Mao, L.-B. Qu, *RSC Adv.* 2013, **3**, 3869.

10 (a) J. Feng, S. Liang, S.-Y. Chen, J. Zhang, S.-S. Fu, X.-Q. Yu, *Adv. Synth. Catal.* 2012, **354**, 1287; (b) S. Wang, J. Wang, R. Guo, G. Wang, S.-Y. Chen, X.-Q. Yu. *Tetrahedron Lett.* 2013, **54**, 6233; (c) G. Wang, Q.-Y. Yu, J. Wang, S. Wang, S.-Y. Chen, X.-Q. Yu, *RSC Adv.* 2013, **3**, 21306.

11 Screening conditions see table S1 in the support information.

12 For secondary or tertiary keto-amide formation from methyl ketones see: (a) F.-T. Du, J.-X. Ji, *Chem. Sci.*, 2012, **3**, 460; (b) W.-P. Mai, H.-H. Wang, Z.-C. Li, J.-W. Yuan, Y.-M. Xiao, L.-R. Yang, P. Mao, L.-B. Qu, *Chem. Commun.*, 2012, **48**, 10117; (c) W. Wei, Y. Shao, H. Hu, F. Zhang, C. Zhang, Y. Xu, X. Wan, *J. Org. Chem.*, 2012, **77**, 7157.

13 (a) L. Gan, S. Huang, X. Zhang, A. Zhang, B. Cheng, H. Cheng, X. Li, G. Shang, *J. Am. Chem. Soc.* 2002, **124**, 13384; (f) C. M. Jones, M. J. Burkitt, *J. Am. Chem. Soc.* 2003, **125**, 6946; (e) W.-J. Yoo, C.-J. Li, *J. Am. Chem. Soc.* 2006, **128**, 13064; (b) L. U. Nordstrøm, H. Vogt, R. Madsen, *J. Am. Chem. Soc.* 2008, **130**, 17672; (c) T. Zweifel, J. V. Naubron, H. Grtzmacher, *Angew. Chem. Int. Ed.* 2009, **48**, 559; (d) J. Zhang, S. Muthaiah, S. C. Ghosh, S. H. Hong, *Angew. Chem. Int. Ed.* 2010, **49**, 6391.