J|A|C|S COMMUNICATIONS

Published on Web 09/16/2006

Highly Efficient Oxidative Amidation of Aldehydes with Amine Hydrochloride Salts

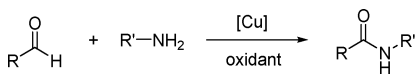
Woo-Jin Yoo and Chao-Jun Li*

Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

Received July 6, 2006; E-mail: cjli@mcgill.ca

The amide functional group is ubiquitous in organic chemistry and is an important motif in polymers, natural products, and pharmaceuticals.[1] The most prevalent strategy for amide bond formation relies heavily upon the interconverison of activated carboxylic acid derivatives with an amine.[2] However, due to the lability of activated carboxylic acid derivatives, alternative strategies toward the synthesis of amides have been explored. Examples include the utilization of azides as amine equivalents in the modified Staudinger reaction,[3] hydrative amide syntheses with alkynes,[4] and thio acid/ester ligation method.[5] Transition-metal-catalyzed carbonylation of alkenes,[6] alkynes,[7] and haloarenes[8] with amines has also been employed for amide synthesis. Finally, the direct utilization of the acyl C−H of aldehydes under oxidative conditions with amines can also serve as an attractive entry into amides.[9] Progress into this methodology has been hampered thus far due to limitations, such as the need for expensive transition-metal catalyst and poor substrate scope.

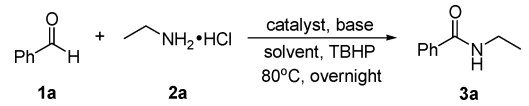
Recently, we reported a copper-catalyzed stereoselective oxidative esterification of aldehydes with β-dicarbonyl compounds using *tert*-butyl hydroperoxide (TBHP) as an oxidant.[10] In light of our recent success in that oxidative esterification reaction, we turned our attention to the much more challenging amidation reaction of simple aldehydes and amines. Herein, we present an efficient copper-catalyzed oxidative amidation protocol between aldehydes and amines (eq 1).



(1)

At the onset of the research, we made a conscious effort to develop a catalytic system that would address the limitations of the previously reported oxidative amidation reactions. During the preliminary studies with the CuBr/TBHP system, the oxidative amidation of aldehydes with primary amines was met with little success partly due to the competing oxidation reaction of the amine. We rationalized that the corresponding amine hydrochloride salt would be resistant to oxidation, and therefore, optimization studies were performed with benzaldehyde **1a** and ethylamine hydrochloride **2a** as substrates (Table 1). After screening a variety of copper salts, CuI was determined to be the most effective catalyst to generate the desired amide **3a**. The addition of a base improved the reaction significantly, with inorganic bases such as $NaHCO_3$ providing the best yields (entries 2 and 3). The reaction conditions were improved slightly with the introduction of $AgIO_3$ additive. The introduction of a solvent did not improve the oxidative amidation reaction (entries 5 and 6). Surprisingly, when the catalyst loading was reduced, amide formation increased significantly and a quantitative yield of amide **3a** was obtained (entries 7 and 8). However, when the scope of the reaction was explored, we quickly discovered that only simple aliphatic amines were viable under the optimized reaction conditions. For example, glycine ethyl ester proved to be a poor substrate, and a variety of side product formation was observed. Thus, further optimization studies were performed in order to develop a better catalytic system that was more functional group compatible (Table 2).

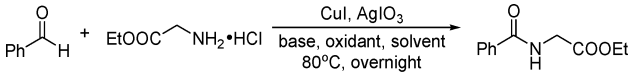
Table 1. Optimization of the Oxidative Amidation of Aldehydes with Amine Hydrochloride Salts[a]



entry	catalyst	base	solvent	yield (%)[b]
1	CuI			35[c]
2	CuI	Et_3N		42
3	CuI	$NaHCO_3$		72
4	CuI, $AgIO_3$	$NaHCO_3$		78
5	CuI, $AgIO_3$	$NaHCO_3$	MeCN	73
6	CuI, $AgIO_3$	$NaHCO_3$	H_2O	68
7	CuI, $AgIO_3$	$NaHCO_3$		90[d]
8	CuI, $AgIO_3$	$NaHCO_3$		99[e]

[a] Benzaldehyde (1.0 equiv), ethylamine HCl (1.5 equiv), base (1.1 equiv), TBHP ($C = 5.5$ M in decane, 1.1 equiv), and catalyst (5.0 mol %) in solvent ($C = 5.0$ M). [b] Reported yields were based on benzaldehyde and determined by NMR using an internal standard. [c] After addition of sat. $NaHCO_3$ solution. [d] CuI (2.5 mol %), $AgIO_3$ (2.5 mol %). [e] CuI (1.0 mol %), $AgIO_3$ (1.0 mol %).

Table 2. Optimization of the Copper-Catalyzed Oxidative Amidation of Aldehydes with Amine Hydrochloride Salts[a]



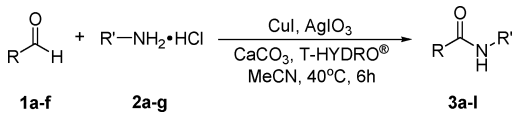
entry	base	solvent	oxidant	yield (%)[b]
1	$NaHCO_3$		TBHP	39
2	$CaCO_3$		TBHP	35
3	$CaCO_3$	MePh	TBHP	50
4	$CaCO_3$	H_2O	TBHP	44
5	$CaCO_3$	MeCN	TBHP	69
6	$CaCO_3$	MeCN	T-HYDRO	93

[a] Benzaldehyde (1.0 equiv), glycine ethyl ester HCl (1.5 equiv), base (1.1 equiv), oxidant (1.1 equiv), CuI (1.0 mol %), and $AgIO_3$ (1.0 mol %) in solvent ($C = 5.0$ M). [b] Reported yields were based on benzaldehyde and determined by NMR using an internal standard.

From control studies, we quickly established that the base was the cause for the undesirable side reactions. Unfortunately, from our previous optimization studies, the base was shown to be critical for the success of the amidation reaction. Thus, we attempted to utilize a very insoluble base, such as $CaCO_3$ (entry 2). Although the yield of amide **3g** was low using $CaCO_3$ as a base, the reaction was clean. Solvents were then introduced into the system in order to provide a medium for efficient stirring (entries 3−5). The most dramatic improvement was observed when the solvent in the oxidant

10.1021/ja064315b CCC: $33.50

Table 3. Copper-Catalyzed Oxidative Amidation of Aldehydes with Amine Hydrochloride Salts[a]



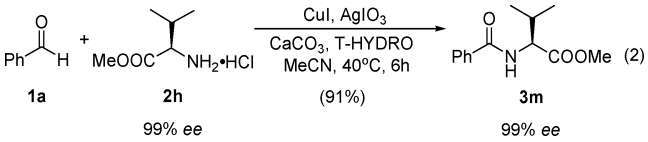
entry	aldehyde	R	amine HCl	R′	product	yield (%)[b]
1	**1a**	Ph	**2a**	Et	**3a**	91
2	**1a**	Ph	**2b**	Bn	**3b**	71
3	**1a**	Ph	**2c**	CH_2Bn	**3c**	89
4	**1a**	Ph	**2d**	cyclohexyl	**3d**	73
5	**1a**	Ph	**2e**	^{t}Bu	**3e**	39
6	**1a**	Ph	**2f**	CH_2CH_2Cl	**3f**	89
7	**1a**	Ph	**2g**	CH_2COOEt	**3g**	91
8	**1b**	4-Me−C_6H_4	**2g**	CH_2COOEt	**3h**	91
9	**1c**	4-MeO−C_6H_4	**2g**	CH_2COOEt	**3i**	78
10	**1d**	4-Cl−C_6H_4	**2g**	CH_2COOEt	**3j**	81
11	**1e**	4-NO_2−C_6H_4	**2g**	CH_2COOEt	**3k**	49
12	**1f**	cyclohexyl	**2g**	CH_2COOEt	**3l**	39

[a] Aldehyde (1.0 equiv), amine HCl (1.5 equiv), $CaCO_3$ (1.1 equiv), T-HYDRO (1.1 equiv), CuI (1.0 mol %), and $AgIO_3$ (1.0 mol %) in MeCN (C = 5.0 M). [b] Isolated yields were based on the aldehyde.

was switched from decane to water (entry 6).[11] The reaction conditions were further optimized, and the reaction was shown to be complete in 6 h at 40 °C.

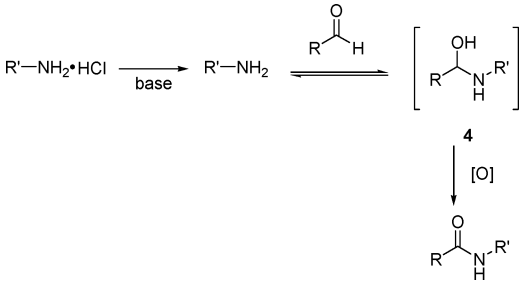
With the further optimized conditions in hand, we explored the scope of the oxidative amidation reaction of aldehydes **1a**−**f** with amine hydrochloride salts **2a**−**g** (Table 3).

Generally, the copper-catalyzed amidation reaction proceeds well to provide the desired amides **3a**−**l** in high yields. Steric effects of the amine HCl salts may play a role since a bulky group, such as ^{t}Bu, provided amide **3e** in low yield (entry 5).[12] Remarkably, the amidation occurred even in the presence of other electrophiles, such as alkyl chloride (entry 6) and ester (entries 7−12). The oxidative amidation was also compatible with a variety of electron-rich and electron-poor aryl aldehydes (entries 8−11). When aliphatic aldehyde **1f** was utilized as a coupling partner, the desired amide **3l** was obtained with a low yield (entry 12). Interestingly, when the oxidative amidation reaction was applied to optically active amine ester **2h**, the reaction proceeded smoothly in high yield without racemization (eq 2).



A tentative mechanism for the oxidative amidation of aldehydes for amide formation is proposed in Scheme 1. The oxidative amidation of the aldehyde may be envisioned by the initial deprotonation of the amine HCl salt to the free amine. Nucleophilic addition of the free amine to aldehyde would generate carbinolamine intermediate **4**, which then may be oxidized by Cu(I)/TBHP to generate the desired amide products.[13,14] Mechanistically, it is also plausible that amide formation may arise from a transamidation reaction with a carboxylic acid derived from the direct oxidation of the aldehyde. However, when benzaldehyde was replaced with benzoic acid, the expected amide was not observed under the optimized reaction conditions.

Scheme 1. Tentative Mechanism for the Oxidative Amidation of Aldehydes with Amine HCl Salts



In conclusion, we have developed an efficient copper-catalyzed protocol for the formation of amides from aldehydes and amine HCl salts using TBHP as an oxidant. Further investigations into the scope, mechanism, and synthetic application of this reaction are now in progress.

Acknowledgment. We thank the Canada Research Chair (Tier I) foundation (to C.J.L.), the CFI, NSERC, and CIC (AstraZeneca/Boehringer Ingelheim/Merck Frosst) for support of our research.

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

References

(1) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.
(2) Larock, R. C. *Comprehensive Organic Transformation*; VCH: New York, 1999.
(3) (a) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007. (b) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939. (c) Damkaci, F.; DeShong, P. *J. Am. Chem. Soc.* **2003**, *125*, 4408.
(4) (a) Cho, S.; Yoo, E.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046. (b) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 1.
(5) (a) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. *Science* **1994**, *266*, 776. (b) Shangguan, N.; Katukojvala, S.; Greenerg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754. (c) Merkx, R.; Brouwer, A. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005**, *7*, 1125.
(6) Beller, M.; Cornils, B.; Frohning, C. D. *J. Mol. Catal. A: Chem.* **1995**, *104*, 17.
(7) (a) Ali, B. E.; Tijani, J. *Appl. Organomet. Chem.* **2003**, *17*, 921. (b) Knapton, D. J.; Meyer, T. Y. *Org. Lett.* **2004**, *6*, 687. (c) Uenoyama, Y.; Fukuyama, T.; Nobuta, O.; Matsubara, H.; Ryu, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 1075.
(8) For recent examples, see: (a) Lin, Y.-S.; Alper, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 779. (b) Uozumi, Y.; Arii, T.; Watanabe, T. *J. Org. Chem.* **2001**, *66*, 5272. (c) Nanayakkara, P.; Alper, H. *Chem. Commun.* **2003**, 2384.
(9) (a) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* **1983**, 474. (b) Naota, T.; Murahashi, S. *Synlett* **1991**, 693. (c) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523.
(10) Yoo, W.-J.; Li, C.-J. *J. Org. Chem.* **2006**, *71*, 6266.
(11) T-HYDRO is the trademark name of a *tert*-butyl hydroperoxide solution in water (70 wt % in H_2O).
(12) Oxidative amidation of aldehydes with secondary amine HCl salts, such as piperidine HCl, did not occur under the current optimized reaction conditions.
(13) Analogous to carbinolamine **4**, oxidation of hemiacetal intermediates has been invoked for the oxidative esterification of aldehydes with alcohols. See: Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 577.
(14) The oxidative amidation reaction most likely occurs via a radical mechanism since radical scavenger, 2,6-di-*tert*-butyl-4-methylphenol (BHT), inhibits the reaction. Radical-based mechanisms have been proposed for the oxidation of alcohols to aldehydes by galactose oxidases. For recent mechanistic studies, see: (a) Himo, F.; Eriksson, L. A.; Maseas, F.; Siegbahn, P. E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8031. (b) Whittaker, M. M.; Ballou, D. P.; Whittaker, J. W. *Biochemistry* **1998**, *37*, 8426. (c) Wachter, R. M.; Montague-Smith, M. P.; Branchaud, B. P. *J. Am. Chem. Soc.* **1997**, *119*, 7743.

JA064315B