Tetrahedron Letters 55 (2014) 3192–3194

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Transition metal-free synthesis of primary amides from aldehydes and hydroxylamine hydrochloride

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ARTICLE INFO

Article history:
Received 3 December 2013
Revised 21 March 2014
Accepted 8 April 2014
Available online 13 April 2014

Keywords:
Aldehyde
Transition metal-free
Primary amide

ABSTRACT

Primary aromatic amides can be synthesized from aldehydes and hydroxylamine hydrochloride in the presence of Cs_2CO_3. Various aromatic aldehydes (include some heteroaromatic aldehydes) are able to generate the corresponding aromatic amides in moderate to excellent yields.

Primary amides play an important role in organic and pharmaceutical chemistry due to their highly useful applications in academia and industry.[1] A large amount of natural products and pharmaceuticals were constructed by peptide bond.[2] Traditional construction methods of primary amides usually adopted coupling of carboxylic acid or its derivatives with ammonia.[3] It has attracted great attention of many synthetic chemists to develop new effective methods for the synthesis of primary amide.[4] In recent years, significant advancement has been achieved in the synthesis of primary amides. With this strategy, primary amides were usually prepared by conversion of benzaldehydes with hydroxylamine[5] or catalytic hydration of organonitriles.[6] Transition metals (Ru, Rh, Pd, Pt, Ir, Au, Fe, Co, Ni, and Cu, etc.) are needed as catalysts for effective conversion in this system,[5,6] nevertheless, nowadays those expensive and toxic transition-metals are out of fashion in industrial applications considering the environmental issues.[7] Therefore, novel economy and environment-friendly catalysis systems are rapidly desired. Bio glycerol-based carbon was used as a recyclable catalyst for a mild and expeditious synthesis of amides from aldehydes.[8] Efficient and practical transition metal-free catalytic hydration of organonitriles to amides has been developed.[9] This significant advance inspired us to explore appropriate catalytic synthesis approach of amides from nontoxic substrates and reagents. In this Letter, a transition-metal-free approach will be described for transformation of aldehydes to primary amides using hydroxylamine hydrochloride with Cs_2CO_3 as catalyst.

Initially, benzaldehyde as model substrate was tested to react with hydroxylamine hydrochloride in various solvents under air conditions. A rough survey of reaction condition indicated that the yields of the catalysis products were largely dependent on the volume ratio of mixed solvent DMSO/H_2O and the base (Table 1). A 19% yield of benzamide was obtained in DMSO at 125 °C in the presence of 1.2 equiv Cs_2CO_3. By using the same conditions, no product was generated in aqueous solution. For instance, the yield of benzamide increased to 54% in the mixed solvent of DMSO and H_2O (v/v = 1/1). Remarkably, while the appropriate proportion of DMSO and H_2O mixture solvent was equal to 3:1 in volume, the highest yield reached up to 91%. Meanwhile, several bases were examined in the following experiments. Under the above conditions, the moderate to good yield of benzamide was obtained by reactions using Cs_2CO_3 as base.

Furthermore, the substrate scope of this reaction was screened by different aromatic aldehydes. Under the optimized conditions, most substituted aldehydes could transform into the corresponding amides (Table 2). In all cases, the corresponding primary benzamides were isolated in moderate to good chemical yields. The substituent can be an electron-donating group such as Me, MeO, or PhO and also be an electron-withdrawing group such as Cl, Br, I, or NO_2. And it can be located at the 3- or 4- position (entries 1–12). Furthermore, the 2-naphthaldehyde (entry 13) and the heteroaromatic aldehydes such as pyridine-2-carbaldehyde (entry 14), furan-2-carbaldehyde (entry 15), thiophene-2-carbaldehyde (entry 16), and substituted heteroaromatic aldehydes (entries 17–20) can be extended to heteroaromatic amides in excellent yields (93–99% yields).

When the reaction of benzaldehyde with hydroxylamine was shortened to 24 h under the optimized conditions, the uncompleted

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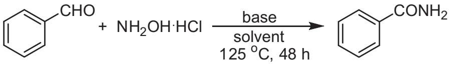
http://dx.doi.org/10.1016/j.tetlet.2014.04.020

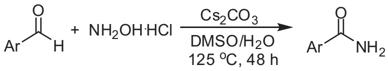
Table 1
Optimization of reaction conditions

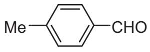
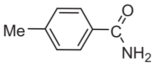
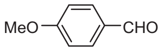
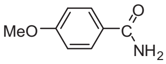
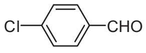
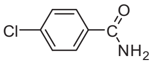
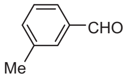
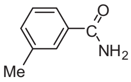
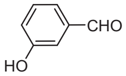
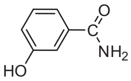
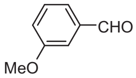
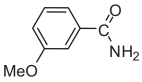
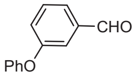
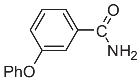
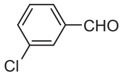
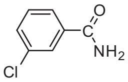
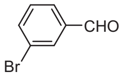
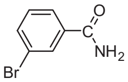
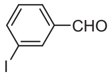
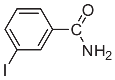
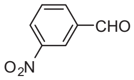
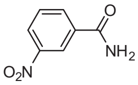
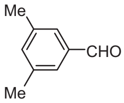
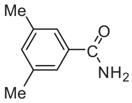
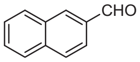
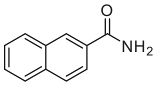
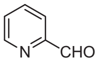
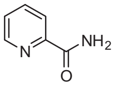
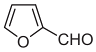
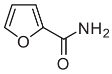
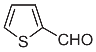
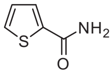
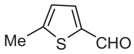
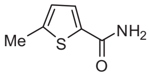
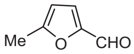
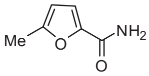
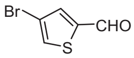
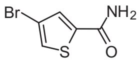
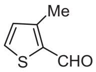
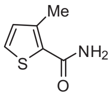


Entry[a]	Solvent	Base	Yield[b]/%
1	DMSO	Cs_2CO_3	19
2	H_2O	Cs_2CO_3	n.r.
3	$DMSO/H_2O$ (1:1)	Cs_2CO_3	54
4	$DMSO/H_2O$ (1:3)	Cs_2CO_3	33
5	$DMSO/H_2O$ (3:1)	Cs_2CO_3	91
6	$DMSO/H_2O$ (3:1)	K_2CO_3	58
7	$DMSO/H_2O$ (3:1)	Na_2CO_3	Trace
8	$DMSO/H_2O$ (3:1)	*t*-BuOK	30
9	$DMSO/H_2O$ (3:1)	NaOH	n.r.
10	$DMSO/H_2O$ (3:1)	$K_3PO_4 \cdot H_2O$	n.r.
11	$DMSO/H_2O$ (3:1)	$NaHCO_3$	n.r.
12	$DMSO/H_2O$ (3:1)	KOAc	n.r.
13	$DMSO/H_2O$ (3:1)	DBU	Trace
14	$DMSO/H_2O$ (3:1)	$K_3PO_4 \cdot 3H_2O$	n.r.

[a] Reaction conditions: benzaldehyde (0.5 mmol), hydroxylamine hydrochloride (0.6 mmol), base (0.6 mmol), solvent (2.0 mL), $T = 125$ °C, $t = 48$ h, under air.
[b] Isolated yield.

Table 2
Synthesis of primary benzamides from various aldehydes[10]



Entry[a]	Substrate	Product	Yield[b]/%
1			52
2			79
3			42
4			49
5			50
6			47
7			91
8			71
9			56
10			66
11			48
12			57
13			99
14			93
15[c]			>99
16[c]			>99
17[d]			>99
18[d]			>99
19[d]			98
20[e]			95

[a] Reaction conditions: aldehyde (0.5 mmol), hydroxylamine hydrochloride (0.6 mmol), Cs_2CO_3 (0.6 mmol), solvent (2.0 mL), $T = 125$ °C, $t = 48$ h, under air.
[b] Isolated yield.
[c] 12 h.
[d] 14 h.
[e] 16 h.

reaction liquid was separated by silica gel column chromatography. GC–MS was used to analyze the composition of the separated product. The mass spectroscopy showed the $m/z = 103$, which is consistent with benzonitrile. On the base of these results, we propose one possible mechanism to allow that the aldehyde first undergo reaction with hydroxylamine hydrochloride in the presence of base to give aldoximes that are transformed into amide by dehydration and hydration processes.[5m]

In conclusion, a simple transition metal-free system was explored to synthesize the primary aromatic amides from aldehydes and hydroxylamine hydrochloride in the presence of Cs_2CO_3. Various aromatic aldehydes are able to generate the corresponding aromatic amides in moderate to excellent yields. The base Cs_2CO_3 and the volume ratio of mixed solvent $DMSO/H_2O$ were important factors in this system. We believe that this transition metal-free system will be useful for the synthesis of primary amides.

Acknowledgment

Financial support from National Science Foundation of China (Nos. 21102135, 21272217 and J1210060) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.020.

References and notes

1. (a) Mabermann, C. E. In *Encyclopedia of Chemical Technology*; Kroschwitz, J. I., Ed.; Wiley: New York, 1991; Vol. 1, pp 251–266; (b) Lipp, D. In *Encyclopedia of Chemical Technology*; Kroschitz, J. I., Ed.; Wiley: New York, 1991; Vol. 1, pp 266–287; (c) Opsahl, R. In *Encyclopedia of Chemical Technology*; Kroschwitz, J. I., Ed.; Wiley: New York, 1991; Vol. 2, pp 346–356.
2. (a) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243; (b) Bode, J. W. *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765; (c) Cupido, T.; Tulla-Puche, J.; Spengler, J.; Albericio, F. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 768.
3. Khalafi-Nezhad, A.; Parhami, A.; Rad, M. N. S.; Zarea, A. *Tetrahedron Lett.* **2005**, *46*, 6879.
4. (a) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447; (b) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827; (c) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606; (d) Hosseini-Sarvari, M.; Sharghi, H. *J. Chem. Res.* **2006**, 205.
5. (a) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* **1983**, 474; (b) Naota, T.; Murahashi, S.-I. *Synlett* **1991**, 693; (c) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523; (d) Chan, W.-K.; Ho, C.-M.; Wong, M.-K.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 14796; (e) Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 13064; (f) Suto, Y.; Yamagiwa, N.; Torisawa, Y. *Tetrahedron Lett.* **2008**, *49*, 5732; (g) Seo, S.; Marks, T. J. *Org. Lett.* **2008**, *10*, 317; (h) Allen, C. L.; Lapkin, A. A.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 4262; (i) Qian, C.; Zhang, X.; Li, J.; Xu, F.; Zhang, Y.; Shen, Q. *Organometallics* **2009**, *28*, 3856; (j) Li, J.; Xu, F.; Zhang, Y.; Shen, Q. *J. Org. Chem.* **2009**, *74*, 2575; (k) Allen, C. L.; Davulcu, S.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 5096; (l) Gowda, R. R.; Chakraborty, D. *Eur. J. Org. Chem.* **2011**, 2226; (m) Ali, M. A.; Punniyamurthy, T. *Adv. Synth. Catal.* **2010**, *352*, 288; (n) Fujiwara, H.; Ogasawara, Y.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 5202.
6. (a) Breslow, R.; Fairweather, R.; Keana, J. *J. Am. Chem. Soc.* **1967**, *89*, 2135; (b) Villain, G.; Gaset, A.; Kalck, P. *J. Mol. Catal.* **1981**, *12*, 103; (c) Murahashi, S.-I.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57*, 2521; (d) Kim, J. H.; Britten, J.; Chin, J. *J. Am. Chem. Soc.* **1993**, *115*, 3618; (e) Ghaffar, T.; Parkins, A. W. *Tetrahedron Lett.* **1995**, *36*, 8657; (f) Kaminskaia, N. V.; Kostić, N. M. *J. Chem. Soc., Dalton Trans.* **1996**, 3677; g Sebti, S.; Rhihil, A.; Saber, A.; Hanafi, N. *Tetrahedron Lett.* **1996**, *37*, 6555; (h) Djoman, M. C. K.-B.; Ajjou, A. N. *Tetrahedron Lett.* **2000**, *41*, 4845; (i) Ghaffar, T.; Parkins, A. W. *J. Mol. Catal. A: Chem.* **2000**, *160*, 249; (j) Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771; (k) Mascharak, P. K. *Coord. Chem. Rev.* **2002**, *225*, 201; (l) Jiang, X.-B.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Org. Chem.* **2004**, *69*, 2327; (m) Yamaguchi, K.; Matsushita, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1576; (n) Goto, A.; Endo, K.; Saito, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3607; (o) Mitsudome, T.; Mikami, Y.; Mori, H.; Arita, S.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Chem. Commun.* **2009**, 3258; (p) Polshettiwar, V.; Varma, R. S. *Chem.-Eur. J.* **2009**, *15*, 1582; (q) Ramón, R. S.; Marion, N.; Nolan, S. P. *Chem.-Eur. J.* **2009**, *15*, 8695; (r) Yamaguchi, K.; Mizuno, N. *Synlett* **2010**, 2365; (s) Ahmed, T. J.; Knapp, S. M. M.; Tyler, D. R. *Coord. Chem. Rev.* **2011**, *255*, 949; (t) Kim, A. Y.; Bae, H. S.; Park, S.; Park, S.; Park, K. H. *Catal. Lett.* **2011**, *141*, 685.
7. (a) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233; (b) Punniyamurthy, T.; Rout, L. *Coord. Chem. Rev.* **2008**, *252*, 134.
8. Ramesh, K.; Murthy, S. N.; Karnakar, K.; Reddy, K. H. V.; Nageswar, Y. V. D.; Vijay, M.; Devi, B. L. A. P.; Prasad, R. B. N. *Tetrahedron Lett.* **2012**, *53*, 2636.
9. (a) Tu, T.; Wang, Z.; Liu, Z.; Feng, X.; Wang, Q. *Green Chem.* **2012**, *14*, 921; (b) Chill, S. T.; Mebane, R. C. *Synth. Commun.* **2010**, *40*, 2014.
10. *General procedure for conversion of aldehydes to primary amides:* Aldehyde (0.5 mmol), $NH_2OH\cdot HCl$ (0.6 mmol) and Cs_2CO_3 (0.6 mmol) were stirred at 125 °C for 48 h in a 3:1 mixture of DMSO–H_2O (2 mL) under air. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the reaction mixture was cooled to room temperature and treated with water (1 mL). The resulting mixture was extracted with ethyl acetate (3 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane. The purified products were identified by ^1H NMR spectra and the melting points comparison with the literature data.