JOC*Note*

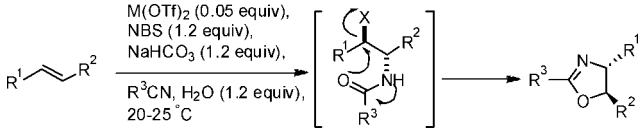
Stereoselective One-Pot Synthesis of Oxazolines

Saumen Hajra,* Sukanta Bar, Debarshi Sinha, and Biswajit Maji

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

shajra@chem.iitkgp.ernet.in

Received February 18, 2008



Treatment of alkenes with NBS, a nitrile, $NaHCO_3$ and water in the presence of $Cu(OTf)_2$ or $Zn(OTf)_2$ is reported to furnish oxazolines in one pot and good yields. The reaction is equally applicable to chalcones.

Oxazolines are frequently found in biologically active natural products and pharmaceuticals.[1,2] Their chiral derivatives are widely used as ligands or chiral pools in asymmetric synthesis.[3] Achiral oxazolines are also valuable intermediates in organic synthesis[4] and polymer chemistry.[5] Consequently, many methods exist in the literature for their synthesis.[6–8] The majority of the methods involve prior preparation of precursor 1,2-amino alcohols.[6] Recently, multicomponent reactions have been reported for the synthesis.[7] Alternatively, oxazolines are prepared by cyclization of β-haloamides **2**, which in turn are obtained by haloamidation reaction of alkenes **1** (Scheme 1). However, selective haloamidation reactions of alkenes are little explored.[9] Recently, an efficient method for the haloamidation of cyclohexenes was reported.[10]A one-pot synthesis[11] of oxazolines from

SCHEME 1. Synthesis of Oxazolines via Haloamidation Reaction

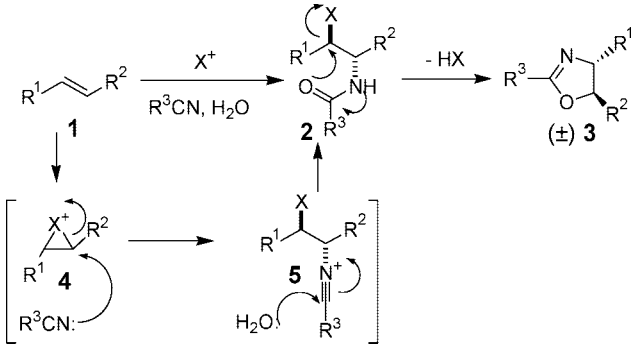
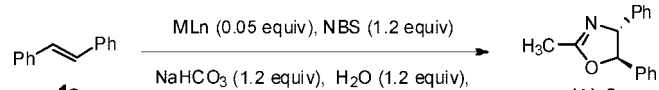


TABLE 1. Synthesis of Oxazoline 3a from Stilbene 1a



entry	MLn	conv (%)[a]	yield of **3a** (%)[a]
1	none	0	0
2	$NiCl_2$	0	0
3	$MgCl_2$	0	0
4	$Mg(OTf)_2$	0	0
5	Cu_2Cl_2	10	<5
6	$Sm(OTf)_3$	25	<5
7	$Yb(OTf)_3$	30	<10
8	$Y(OTf)_3$	32	<15
9	$Sc(OTf)_3$	35	<15
10	$FeCl_3$	100	40 (35)
11	$CuCl_2$	100	40 (35)
12	$Zn(OTf)_2$	100	66 (15)
13	$Cu(OTf)_2$	100	67 (15)

[a] Determined from the ^1H NMR spectra of the crude reaction mixture with succinic anhydride as an internal standard; yields in the parentheses refer to the yield of dibromide of *trans*-stilbene.

(1) (a) Bergeron, R. J. *Chem. Rev.* **1984**, *84*, 587–602. (b) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771–1791. (c) Penke, B.; Toth, G.; Varadi, G. *Amino Acids, Peptides, Proteins* **2006**, *35*, 129–271. (d) Hsiue, G.-H.; Wang, C.-H.; Lo, C.-L.; Wang, C.-H.; Li, J.-P.; Yang, J.-L. *Int. J. Pharm.* **2006**, *317*, 69–75.

(2) (a) Nicolaou, K. C.; Liazos, D. E.; Kim, D. W.; Schlawe, D.; de Noronha, R. G.; Longbottom, D. A.; Rodriguez, M.; Bucci, M.; Cirino, G. *J. Am. Chem. Soc.* **2006**, *128*, 4460–4470. (b) Pirrung, M. C.; Tumey, L. N.; McClerren, A. L.; Ratz, C. R. H. *J. Am. Chem. Soc.* **2003**, *125*, 1575–1586. (c) Bode, H. B.; Irsch, H.; Wenzel, S. C.; Reichenbach, H.; Muller, R.; Hofle, G. *J. Nat. Prod.* **2003**, *66*, 1203–1206. (d) Kline, T.; Anderson, N. H.; Harwood, E. A.; Bowman, J.; Malanda, A.; Endsley, S.; Erwin, A. l.; Doyle, M.; Fong, S.; Harris, A. L.; Mendelsohn, B.; Mdluli, K.; Raetz, C. R. H.; Stover, C. K.; Witte, P. R.; Yabannavar, A.; Zhu, S *J. Med. Chem.* **2002**, *45*, 3112–3129.

(3) For recent reviews, see: (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335. (c) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345.

(4) For representative reviews, see: (a) Frump, J. A. *Chem. Rev.* **1971**, *71*, 483–505. (b) Meyers, A. I.; Reuman, M. *Tertrahedron* **1985**, *41*, 837–860. (c) Meyers, A. I.; Gant, T. *G Tetrahedron* **1994**, *50*, 2297–2360.

(5) (a) Huang, H.; Hoogenboom, R.; Leenen, M. A. M.; Guillet, P.; Jonas, A. M.; Schubert, U. S.; Gohy, J.-F. *J. Am. Chem. Soc.* **2006**, *128*, 3784–3788. (b) Kobayashi, S.; Fujikawa, S.-I.; Ohmae, M. *J. Am. Chem. Soc.* **2003**, *125*, 14357–14369. (c) Hseih, D. T.; Peiffer, D. G. *J. Appl. Polym. Sci.* **1995**, *56*, 1667–1671. (d) Kaku, M.; Hung, M. H. *Macromolecules* **1993**, *26*, 6135–6137. (e) Cai, G.; Litt, M. H. *Macromolecules* **1992**, *25*, 2277–2279.

(6) For examples, see: (a) Schwekendiek, K.; Glorius, F. *Synthesis* **2006**, *18*, 2996–3002. (b) Ohshima, T.; Iwasaki, T.; Mashima, K. *Chem. Commun.* **2006**, 2711–2713. (c) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2002**, *4*, 3399–3401. (d) Wuts, P. G. M.; Northuis, J. M.; Kwan, T. A. *J. Org. Chem.* **2000**, *65*, 9223–9225. (e) Elliot, P. M. C.; Druiswijk, E. J. *Chem. Commun.* **1997**, 2311–2312. (f) Zhou, P.; Blubaum, J. E.; Burns, C. T.; Natale, N. R. *Tetrahedron Lett.* **1997**, *38*, 7019–7020. (g) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron. Lett.* **1990**, *31*, 6005–6008. (h) Witte, H.; Seeliger, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 287–289.

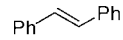
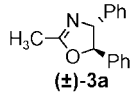
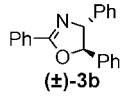
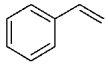
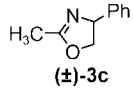
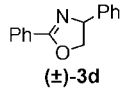
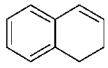
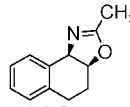
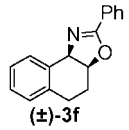
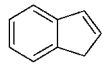
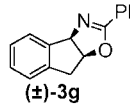
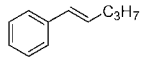
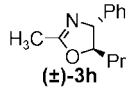
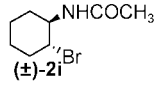
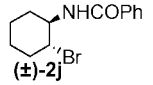
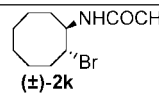
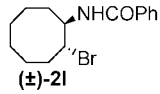
(7) (a) Chaudhry, P.; Schoenen, F.; Neuenswander, B.; Lushington, G. H.; Aube, J. *J. Comb. Chem* **2007**, *9*, 473–476. (b) Fan, L.; Lobkovsky, E.; Ganem, B. *Org. Lett.* **2007**, *9*, 2015–2017. (c) Crosignani, S.; Swinnen, D. *J. Comb. Chem.* **2005**, *7*, 688–696.

(8) (a) Tiecco, M.; Testaferri, L.; Santi, C; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Eur. J. Org. Chem.* **2000**, 3451–3457. (b) Tingoli, M.; Testaferri, L.; Temperini, A.; Tiecco, M. *J. Org. Chem.* **1996**, *61*, 7085–7091. (c) Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *J. Chem. Soc. Perkin Trans. 1* **1989**, 1775–1780. (d) Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *Tetrahedron Lett.* **1988**, *29*, 1049–1052.

(9) (a) Tiecco, M.; Testaferri, L.; Marini, F.; Temperini, A.; Bagnoli, L.; Santi, C. *Synth. Commun.* **1997**, *27*, 4131–4140. (b) Bellucci, G.; Bianchini, R.; Chiappe, C. *J. Org. Chem.* **1991**, *56*, 3067–3073. (c) Hassner, A.; Levy, L. A.; Gault, R. *Tetrahedron Lett.* **1966**, *27*, 3119–3121. (d) Cairns, T. L.; Graham, P. J.; Barrick, P. L.; Schreiber, R. S. *J. Org. Chem.* **1952**, *17*, 751–757.

10.1021/jo8003937 CCC: $40.75 © 2008 American Chemical Society
Published on Web 05/07/2008

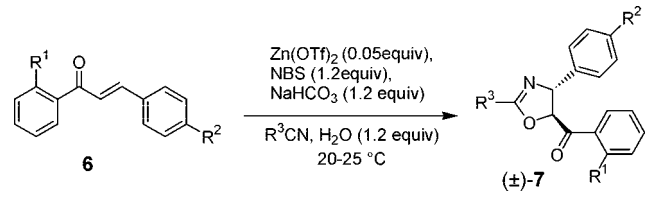
TABLE 2. Cu(OTf)$_2$-Catalyzed Bromoamidation Reaction and One-Pot Synthesis of Oxazolines[a]

entry	alkene **1**	nitrile	*t* (h)	product	yield[b] (%)
1		MeCN	8	 **(±)-3a**	62
2		PhCN	6	 **(±)-3b**	65
3		MeCN	6	 **(±)-3c**	72
4[c]		PhCN	6	 **(±)-3d**	65
5		MeCN	12	 **(±)-3e**	51
6		PhCN	15	 **(±)-3f**	54
7		PhCN	15	 **(±)-3g**	51
8		MeCN	18	 **(±)-3h**	56
9[c]		MeCN	12	 **(±)-2i**	68
10[c]		PhCN	6	 **(±)-2j**	71
11[c]		MeCN	8	 **(±)-2k**	69
12[c]		PhCN	4	 **(±)-2l**	72

[a] Cu(OTf)$_2$ (0.05 equiv)-catalyzed one-pot synthesis of oxazoline was performed with 1.0 equiv of alkene, 1.2 equiv of NBS, 1.2 equiv of $NaHCO_3$, and 1.2 equiv of H_2O in different nitriles at 20–25 °C. [b] Isolated yield of pure oxazoline/haloamide after column chromatography; 10−15% dibromide and 5−10% bromohydrin were obtained. [c] Alkenes were used in excess (5.0 equiv), and NBS was used as a limiting reagent.

alkenes and amides using *t*-BuOI was reported while our study was in progress. Here, we describe a one-pot stereoselective synthesis of oxazolines based on metal triflate catalyzed haloamidation reaction of alkenes with NBS, a nitrile, and water.

TABLE 3. One-Pot Synthesis of Oxazolines from Chalcones[a]



entry	R^1	R^2	R^3	time (h)	conv[b] (%)	product	yield of **7**[c] (%)
1	H	H	Me	12	72	(±)-**7a**	65
2	H	H	Ph	7	100	(±)-**7b**	68
3	H	F	Me	14	70	(±)-**7c**	66
4	H	F	Ph	8	100	(±)-**7d**	69
5	H	Cl	Me	16	72	(±)-**7e**	68
6	H	Cl	Ph	6	100	(±)-**7f**	71
7	OMe	H	Me	8	71	(±)-**7g**	69
8	OMe	H	Ph	5	100	(±)-**7h**	74
9	OMe	F	Ph	5	100	(±)-**7i**	78
10	OMe	Cl	Ph	5	100	(±)-**7j**	76

[a] One-pot synthesis of oxazoline from chalcone **6** (1.0 equiv) was performed with Zn(OTf)$_2$ (0.05 equiv), 1.2 equiv of NBS, 1.2 equiv of $NaHCO_3$ and 1.2 equiv of H_2O in different nitriles at 20−25 °C. [b] Determined from the ^{1}H NMR spectra of the crude reaction mixture with succinic anhydride as internal standard. [c] Isolated yield of the respective oxazoline **7** after column chromatography based on 100% conversion of the alkenes; 8–12% dibromide and 5–10% bromohydrin also formed.

Based on our previous experience,[12] we envisioned that metal triflates might catalyze both the haloamidation of alkenes and the subsequent cyclization to the oxazolines (Scheme 1). Accordingly, we first studied the reaction of stilbene **1a** with NBS in aqueous CH_3CN in the presence of a variety of Lewis acids, and the results are presented in Table 1.

Among the Lewis acids examined, Zn(OTf)$_2$ and Cu(OTf)$_2$ were found to be most effective for the formation of oxazolines (entries 12 and 13). The best result was obtained when substrate **1a** was treated with 0.05 equiv of Cu(OTf)$_2$ [or Zn (OTf)$_2$], 1.2 equiv of NBS, 1.2 equiv of H_2O, and 1.2 equiv of $NaHCO_3$ in CH_3CN at 25 °C, for 8 h. The use of $NaHCO_3$ gave cleaner reactions. Limiting the amount of water to 1.2 equiv was required to minimize the competing formation of bromohydrin. Shorter reaction time led to the formation of a mixture of bromoamide and oxazoline.

To establish the generality of the reaction, we investigated different combinations of alkenes and two nitriles, i.e., acetonitrile and benzonitrile (Table 2). *trans*-Stilbene, styrene, dihydronaphthalene, indene, and β-propylstyrene directly provided the oxazolines **3** with both of the nitriles (entries 1–8). On the other hand, cyclohexene and *cis*-cyclooctene exclusively yielded the bromoamides **2** in good yields, which did not cyclize to give the oxazolines, even on prolonged reaction time (entries 9–12). Treatment with DBU and Et_3N transformed the bromoamides to the corresponding oxazolines.[9] Reactions with benzonitrile were, in general, faster than those with acetonitrile.

(10) Yeung, Y.-Y.; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644–9645.
(11) Minakata, S.; Morino, Y.; Ide, T.; Oderaotoshi, Y.; Komatsu, M. *Chem. Commun.* **2007**, 3279–3281.
(12) (a) Hajra, S; Maji, B.; Bar, S. *Org. Lett.* **2007**, *9*, 2783–2786. (b) Hajra, S.; Bhowmick, M.; Maji, B.; Sinha, D. *J. Org. Chem.* **2007**, *72*, 4872–4876. (c) Hajra, S.; Sinha, D.; Bhowmick, M. *J. Org. Chem.* **2007**, *72*, 852–1855. (d) Hajra, S.; Bhowmick, M.; Sinha, D. *J. Org. Chem.* **2006**, *71*, 9237–9240 (e) Hajra, S.; Sinha, D.; Bhowmick, M. *Tetrahedron Lett.* **2006**, *47*, 7017–7019. (f) Hajra, S.; Bhowmick, M.; Karmakar, A. *Tetrahedron Lett.* **2005**, *46*, 3073–3077.

In order to increase the scope of the reaction, we opted to study the reactivities of the supposedly less nucleophilic alkenes, i.e., chalcones **6** (Table 3). Moreover, haloamidations of α,β-unsaturated ketones are little studied.

When chalcones **6** were subjected to the $Zn(OTf)_2$-catalyzed reaction with NBS (1.2 equiv), H_2O (1.2 equiv) in CH_3CN, or PhCN at 20–25 °C, oxazolines **7** were obtained in moderate to good yields (Table 3). Reactions with acetonitrile were slower, with incomplete conversion even after 12–16 h (entries 1, 3, 5, and 7), whereas reactions in benzonitrile were complete (100% conversion) in 5–8 h (entries 2, 4, 6, and 8–10).

In summary, a general and efficient method is described for one-pot synthesis of oxazolines based on haloamidation of alkenes with NBS and stoichiometric amount of water. This process is catalyzed by Lewis acids. $Cu(OTf)_2$ and $Zn(OTf)_2$ are most effective for the reactions. Chalcones are also suitable for the transformations. Further applications of 1,2-halofunctionalization of alkenes are currently under investigation in our laboratory.

Experimental Section

General Procedure for One-Pot Synthesis of Oxazolines from Alkenes. To a well-stirred solution of an alkene (1.0 equiv) and nitrile (5 mL/mmol), $Cu(OTf)_2$ or $Zn(OTf)_2$ (0.05 equiv), and NBS (1.2 equiv) were added $NaHCO_3$ (1.2 equiv) and H_2O (1.2 equiv) and the mixture allowed to stir at rt (20 to 25 °C) under an argon atmosphere. Progress of the reaction was monitored by TLC. On completion, solvent was evaporated under reduced pressure. The crude reaction mixture was subjected to purification by flash column chromatography using EtOAc/petroleum ether (60−80 °C) as an eluent.

2,4,5-Triphenyl-4,5-dihydrooxazole (3b): gummy liquid; 0.215 g (65%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (2H, d, J = 7.2 Hz), 7.53–7.15 (13H, m), 5.35 (1H, d, J = 7.6 Hz), 5.16 (1H, d, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.0, 141.9, 140.4, 131.7, 128.93 (2C), 128.87 (2C), 128.59 (2C), 128.53 (2C), 128.51, 127.7, 127.4, 126.7 (2C), 125.6 (2C), 88.9, 78.9. Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.39; H, 5.43; N, 4.49.

2-Methyl-3a,4,5,9b-tetrahydronapthol[1,2-*d*]oxazole (3e): gummy liquid; 0.147 g (51%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (1H, d, J = 7.2 Hz), 7.24 (1H, d, J = 6.8 Hz), 7.17 (1H, t, J = 7.2 Hz), 7.11 (1H, d, J = 7.2 Hz), 5.15 (1H, d, J = 9.6 Hz), 5.04–5.0 (1H, m), 2.77–2.69 (1H, m), 2.60–2.54 (1H, m), 2.18–2.08 (1H, m), 1.97 (3H, s), 1.92–1.81(1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 137.9, 134.9, 129.5, 128.2, 127.1, 127.0, 78.4, 66.9, 28.1, 24.4, 13.9. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.18; H, 6.91; N, 7.29.

(2-Methyl-4-phenyl-4,5-dihydrooxazol-5-yl)phenylmethanone (7a): colorless liquid; 0.119 g (65%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (2H, d, J = 8.0 Hz), 7.26 (1H, t, J = 7.6 Hz), 7.45 (2H, t, J = 8.0 Hz), 7.40–7.33 (3H, m), 7.25 (2H, t, J = 1.2 Hz), 5.55 (1H, d, J = 6.8 Hz), 5.23 (1H, d, J = 6.4 Hz), 2.23 (3H, s); ^{13}C NMR($CDCl_3$, 100 MHz) δ 199.4, 169.3, 139.6, 134.3, 133.2, 129.1 (2C), 128.8 (2C), 128.5 (2C), 127.9, 126.9(2C), 75.4, 54.6, 22.9. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.71; H, 5.89; N, 5.61.

(2,4-Diphenyl-4,5-dihydrooxazol-5-yl)phenylmethanone (7b): colorless liquid; 0.213 g (68%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.1 (2H, d, J = 7.2 Hz), 7.94 (2H, d, J = 7.2 Hz), 7.64 (1H, t, J = 7.2 Hz), 7.56–7.31 (10H, m), 5.71 (1H, d, J = 6.4 Hz), 5.52 (1H, d, J = 6.4 Hz); ^{13}C NMR($CDCl_3$, 100 MHz) δ 194.4, 163.8, 140.9, 134.0, 131.7, 129.1 (2C), 129.0 (2C), 128.8 (2C), 128.7 (2C), 128.54, 128.44 (2C), 128.18, 127.0 (2C), 126.8, 86.7, 73.6. Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.91; H, 5.15; N, 4.51.

Acknowledgment. We thank DST, New Delhi, for providing financial support and Prof. D. Mal for helpful suggestions. S.B. and D.S. thank CSIR, New Delhi, and B.M. thanks UGC, New Delhi, for their fellowships.

Supporting Information Available: Spectral data and spectra of oxazolines **3** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8003937