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Xun Zhu* and Yunyang Wei*

An efficient synthesis of 2-substituted benzoxazoles using cerium(III) chloride/sodium iodide as catalyst

Abstract: An efficient and environmentally benign method for the synthesis of 2-substituted benzoxazoles is reported. The condensation of 2-aminophenol with an aldehyde gave an imine intermediate, which was cyclized and dehydrogenated to 2-substituted benzoxazole with good yield in the presence of $CeCl_3$/NaI as catalyst. The one-pot synthesis was carried out in toluene at 100°C using O_2 as the oxidant.

Keywords: cerium(III) chloride; Lewis acid one-pot synthesis; sodium iodide; 2-substituted benzoxazoles.

***Corresponding authors: Xun Zhu and Yunyang Wei,** School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing, P.R. China, e-mail: ywei@mail.njust.edu.cn; zhuxun246@126.com
Xun Zhu: Department of Chemical Engineering, Yancheng Textile Vocational Technology College, Yancheng, P.R. China

Introduction

Recently, cerium(III) chloride has become an attractive candidate as a Lewis acid in organic chemistry for its relative nontoxicity and ready availability (Bartoli et al., 2007). 2-Substituted benzoxazoles are important heterocyclic compounds that have received considerable attention in the field of medicinal chemistry. These heteroaromatic derivatives are commonly encountered in melatonin receptor agonists (Sun et al., 2004), estrogen receptor agonists (Manas et al., 2004), 5-HT_3 receptor agonists (Yoshida et al., 2005), Rho kinase inhibitors (Sessions et al., 2008), and antitumor agents (Aiello et al., 2008). In addition to their use in pharmaceuticals, benzoxazoles are recognized as an important scaffold in agrochemicals and other fine chemicals (Blacker et al., 2009). The widespread interest in benzoxazole-containing structures has promoted extensive studies for their synthesis.

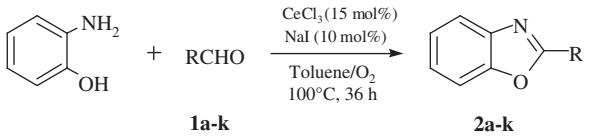
A conventional method for the synthesis of 2-substituted benzoxazoles is the reaction of 2-aminophenol with carboxylic acid derivatives in the presence of strong acid under harsh conditions (Pottorf et al., 2003). Another traditional method for the preparation of benzoxazoles includes the condensation of 2-aminophenols with aldehydes and subsequent oxidative cyclization of the imine intermediate (Osowska and Miljanic, 2011). Recently, methods using transition metal-catalyzed coupling reactions for the construction of benzoxazole framework were also reported, including copper (Kidwai et al., 2006; Ueda and Nagasawa, 2008, 2009; Guru et al., 2011), palladium (Ackermann et al., 2010), iron (Bonnamour et al., 2008), ruthenium, iridium (Blacker et al., 2009), nickel (Canivet et al., 2009), and cobalt-catalyzed (Saha et al., 2010) couplings. Activated carbon (Kawashita et al., 2003) and $ZnBr_2$/ABM (Riadi et al., 2011) have also been used to promote the benzoxazole preparation reactions. Marsden et al. (2008) have reported that 2-arylbenzoxazoles can be synthesized by aza-Wittig reactions.

In the course of our studies on the synthesis of 2-substituted benzoxazoles, it was found that $CeCl_3$/NaI, a system used by Sabitha et al. (2004) for the synthesis of 1,5-benzodiazepines, is an efficient catalyst for the synthesis of the benzoxazole framework from 2-aminophenol and aldehydes (Scheme 1).

Results and discussion

The initial experiments were carried out in toluene using benzaldehyde as the model substrate. Effects of a range of catalysts on the reaction were tested. It was found that in the presence of 15 mol% of $CeCl_3$ and 10 mol% of NaI as catalyst, the yield of 2-phenyl benzoxazole was higher than in other cases (Table 1, entries 1–7). Toluene was found to be the appropriate solvent. When the reaction was carried out in tetrahydrofuran (THF) or 1,4-dioxane, the yield of 2-phenyl-benzoxazole was lower (Table 1, entries 7–9).

Encouraged by the preliminary results, we then studied the scope of the reaction. It was found that both aliphatic aldehydes and aromatic aldehydes react with



1a-k **2a-k**

a: R = H

b: R = $CH_3(CH_2)_2$

c: R = $CH_3(CH_2)_3$

d: R = 4-$NO_2C_6H_4$

e: R = 4-ClC_6H_4

f: R = 4-BrC_6H_4

g: R = 4-$CH_3C_6H_4$

h: R = C_6H_5

i: R = 4-$CH_3OC_6H_4$

j: R = 2-styryl

k: R = 2-furyl

Scheme 1

2-aminophenol to form the corresponding 2-substituted benzoxazoles in the presence of 15 mol% of $CeCl_3$ and 10 mol% of NaI as catalyst (Scheme 1). With aromatic aldehydes as substrates, the reactions proceed smoothly at 100°C with easy workup operation and high product yield (Scheme 1, **2d–j**). The electronic properties of the substituents in the aromatic aldehydes have a remarkable influence on the reaction. The presence of electron-withdrawing groups is beneficial for the reaction and higher yields are obtained. The presence of electron-donating groups reduce the yield of the product (Scheme 1, **2g** and **2i**). With aliphatic aldehydes such as butyraldehyde or valeraldehyde as substrates, moderate to good yields of the corresponding benzoxazoles are also obtained (Scheme 1, **2b**,**c**). With formaldehyde as substrate, a low yield of benzoxazole was obtained, probably due to the presence of H_2O brought to the reaction system with aqueous formaldehyde (Scheme 1, **2a**). The use of heteroaryl aldehydes such as 2-furylcarboxaldehyde also give low yields (Scheme 1, **2k**).

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Yield (%)[b]
1	–	Toluene	100	<5
2	$CuCl_2$ (10)	Toluene	100	15
3	$AlCl_3$ (10)	Toluene	100	20
4	$CeCl_3 \cdot 7H_2O$ (10)	Toluene	100	25
5	$CeCl_3$ (10)	Toluene	100	30
6	$CeCl_3$ (20)	Toluene	100	45
7	$CeCl_3$-NaI (15–10)	Toluene	100	75
8	$CeCl_3$-NaI (15–10)	THF	Reflux	45
9	$CeCl_3$-NaI (15–10)	1,4-Dioxane	Reflux	40

Table 1 Optimization of the synthesis of 2-phenylbenzoxazole[a].
[a]Reaction conditions: 2-aminophenol, 1.2 mmol; benzaldehyde, 1 mmol; solvent, 5 mL; 100°C for 36 h under O_2.
[b]GC-MS yield.

Conclusion

A new method for the synthesis of 2-substituted benzoxazoles from 2-aminophenol and aldehydes in the presence of 15 mol% of $CeCl_3$ and 10 mol% of NaI was developed. The one-pot synthesis is carried out in toluene at 100°C using molecular oxygen as the oxidant. The procedure is suitable for the synthesis of 2-aryl and 2-alkyl-substituted benzoxazoles from 2-aminophenol and aromatic or aliphatic aldehydes.

Experimental

All chemicals (AR grade) were obtained from commercial resources and used without further purification. Gas chromatography (GC) analysis was performed on an Agilent GC-6820 chromatograph equipped with HP-Innowax (30 m×0.32 mm×0.5 μm) capillary column and a flame ionization detector. GC-MS spectra were recorded on Thermo Trace DSQ GC-MS spectrometer using TRB-5MS (30 m×0.25 mm×0.25 μm) column. Melting points were determined using a Yamato melting point apparatus Model MP-21 and are uncorrected. ^{1}H NMR spectra were obtained with TMS as internal standard in $CDCl_3$ using a Bruker DRX 500 (500-MHz) spectrometer. Progress of the reactions was monitored by TLC using silica-gel polygrams SIL G/UV 254 plates. Column chromatography was performed using Silicycle (40–60 mm) silica gel. Products were identified by ^{1}H NMR. All products are known.

General experimental procedure

A solution of 2-aminophenol (1.2 mmol) and benzaldehyde (1 mmol) in toluene (5 mL) was stirred for 20 min at room temperature and then treated with $CeCl_3$ (0.04 g, 0.15 mmol) and NaI (0.015 g, 0.1 mmol). The mixture was stirred at 100°C under O_2 for 36 h. The aqueous solution was extracted with ethyl acetate (3×10 mL), and the product was purified on a small silica gel column with EtOA/petroleum ether (1:9) as eluent.

Benzoxazole (2a) Yield 40%; this compound was obtained as oil (Lee et al., 2009, yield 69%).

2-Propylbenzoxazole (2b) Yield 70%; this compound was obtained as oil (Cho et al., 2002, yield 59%).

2-Butylbenzoxazole (2c) Yield 66%; this compound was obtained as oil (Blacker et al., 2009, yield 52%).

2-(4-Nitrophenyl)benzoxazole (2d) Yield 82%; this compound was obtained as white crystals, mp 271–273°C (Kidwai et al., 2006, yield 75%; mp 270–272°C).

2-(4-Chlorophenyl)benzoxazole (2e) Yield 80%; this compound was obtained as white crystals, mp 152–154°C (Kawashita et al., 2003, yield 88%; mp 153–154°C).

2-(4-Bromophenyl)benzoxazole (2f) Yield 75%. This compound was obtained as white crystals, mp 157–158°C (Guru et al., 2011, yield 81%; mp 157–158°C).

2-(4-Tolyl)benzoxazole (2g) Yield 65%; this compound was obtained as white solid, mp 116–117°C (Ackermann et al., 2010, yield 82%; mp 117–118°C).

2-Phenylbenzoxazole (2h) Yield 73%; this compound was obtained as white crystals, mp 106–108°C (Kawashita et al., 2003, yield 78%; mp 106–107°C).

2-(4-Methoxyphenyl)benzoxazole (2i) Yield 63%; this compound was obtained as white solid, mp 104–106°C (Guru et al., 2011, yield 76%; mp 103–105°C).

2-(2-Styryl)benzoxazole (2j) Yield 89%; this compound was obtained as white solid, mp 86–87°C (Kidwai et al., 2006, yield 86%; mp 86–88°C).

2-(Furan-2-yl)benzoxazole (2k) Yield 42%; this compound was obtained as white solid, mp 88–89°C (Tauer et al., 1981, yield 35%; mp 89–90°C).

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References

Ackermann, L.; Barfuesser, S.; Pospech, J. Palladium-catalyzed direct arylations, alkenylations, and benzylations through C–H bond cleavages with sulfamates or phosphates as electrophiles. *Org. Lett.* **2010**, *12*, 724–726.

Aiello, S.; Wells, G.; Stone, E. L.; Kadri, H.; Bazzi, R.; Bell, D. R.; Stevens, M. F. G.; Matthews, C. S.; Bradshaw, T. D.; Westwell, A. D. Synthesis and biological properties of benzothiazole, benzoxazole, and chromen-4-one analogues of the potent antitumor agent 2-(3,4-dimethoxyphenyl)-5-fluorobenzothiazole (PMX 610, NSC 721648). *J. Med. Chem.* **2008**, *51*, 5135–5139.

Bartoli, G.; Fernández-Bolaños, J. G.; Di Antonio, G.; Foglia, G.; Giuli, S.; Gunnella, R.; Mancinelli, M.; Marcantoni, E.; Paoletti, M. SiO_2-supported $CeCl_3 \cdot 7H_2O$-NaI Lewis acid promoter: investigation into the Garcia Gonzalez reaction in solvent-free conditions. *J. Org. Chem.* **2007**, *72*, 6029–6036.

Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. Synthesis of benzazoles by hydrogen-transfer catalysis. *Org. Lett.* **2009**, *11*, 2039–2042.

Bonnamour, J.; Bolm, C. Iron-catalyzed intramolecular O-arylation: synthesis of 2-aryl benzoxazoles. *Org. Lett.* **2008**, *10*, 2665–2667.

Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. Nickel-catalyzed biaryl coupling of heteroarenes and aryl halides/triflates. *Org. Lett.* **2009**, *11*, 1733–1736.

Cho, C. S.; Kim, D. T.; Zhang, J. Q.; Ho, S.-L.; Kim, T.-J.; Shim, S. C. Tin(II) chloride-mediated synthesis of 2-substituted benzoxazoles. *J. Heterocyclic Chem.* **2002**, *39*, 421–423.

Guru, M. M.; Ali, M. A.; Punniyamurthy, T. Copper(II)-catalyzed conversion of bisaryloxime ethers to 2-arylbenzoxazoles via C–H functionalization/C–N/C–O bonds formation. *Org. Lett.* **2011**, *13*, 1194–1197.

Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. Direct and practical synthesis of 2-arylbenzoxazoles promoted by activated carbon. *Org. Lett.* **2003**, *5*, 3713–3715.

Kidwai, M.; Bansal, V.; Saxena, A.; Aerry, S.; Mozumdar, S. Cu-nanoparticles: efficient catalysts for the oxidative cyclization of Schiffs' bases. *Tetrahedron Lett.* **2006**, *47*, 8049–8053.

Lee, J. J.; Kim, J.; Jun, Y. M.; Lee, B. M.; Kim, B. H. Indium-mediated one-pot synthesis of benzoxazoles or oxazoles from 2-nitrophenols or 1-aryl-2-nitroethanones. *Tetrahedron Lett.* **2009**, *65*, 8821–8831.

Manas, E. S.; Unwalla, R. J.; Xu, Z. B.; Malamas, M. S.; Miller, C. P.; Harris, H. A.; Hsiao, C.; Akopian, T.; Hum, W.-T.; Malakian, K.; Wolfrom, S.; Bapat, A.; Bhat, R. A.; Stahl, M. L.; Somers, W. S.; Alvarez, J. C. Structure-based design of estrogen receptor-β selective ligands. *J. Am. Chem. Soc.* **2004**, *126*, 15106–15119.

Marsden, S. P.; McGonagle, A. E.; McKeever-Abbas, B. Catalytic aza-Wittig cyclizations for heteroaromatic synthesis. *Org. Lett.* **2008**, *10*, 2589–2591.

Osowska, K.; Miljanic, O. S. Oxidative kinetic self-sorting of a dynamic imine library. *J. Am. Chem. Soc.* **2011**, *133*, 724–727.

Pottorf, R. S.; Chadha, N. K.; Katkevics, M.; Ozola, V.; Suna, E.; Ghane, H.; Regberg, T.; Player, M. R. Parallel synthesis of benzoxazoles via microwave-assisted dielectric heating. *Tetrahedron Lett.* **2003**, *44*, 175–178.

Riadi, Y.; Mamouni, R.; Azzalou, R.; Haddad, M. E.; Routier, S.; Guillaumet, G.; Lazar, S. An efficient and reusable heterogeneous catalyst animal bone meal for facile synthesis of benzimidazoles, benzoxazoles, and benzothiazoles. *Tetrahedron Lett.* **2011**, *52*, 3492–3495.

Sabitha, G.; Reddy, G. S. K. K.; Reddy, K. B.; Reddy, N. M.; Yadav, J. S. A new, efficient and environmentally benign protocol for the synthesis of 1,5-benzodiazepines using cerium(III) chloride/sodium iodide supported on silica gel. *Adv. Synth. Catal.* **2004**, *346*, 921–923.

Saha, P.; Ali, M. A.; Ghosh, P.; Punniyamurthy, T. Cobalt-catalyzed intramolecular C–N and C–O cross-coupling reactions: synthesis of benzimidazoles and benzoxazoles. *Org. Biomol. Chem.* **2010**, *8*, 5692–5699.

Sessions, E. H.; Yin, Y.; Bannister, T. D.; Weiser, A.; Griffin, E.; Pocas, J.; Cameron, M. D.; Ruiz, C.; Lin, L.; Schuerer, S. C.; Schroeter, T.; LoGrasso, P.; Feng, Y. Benzimidazole- and benzoxazole-based inhibitors of Rho kinase. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6390–6393.

Sun, L.-Q.; Chen, J.; Bruce, M.; Deskus, J. A.; Epperson, J. R.; Takaki, K.; Johnson, G.; Iben, L.; Mahle, C. D.; Ryan, E.; Xu, C. Synthesis and structure–activity relationship of novel benzoxazole derivatives as melatonin receptor agonists. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3799–3802.

Tauer, E.; Grellmann, K. H. Photochemical and thermal reactions of aromatic Schiff bases. *J. Org. Chem.* **1981**, *46*, 4252–4258.

Ueda, S.; Nagasawa, H. Synthesis of 2-arylbenzoxazoles by copper-catalyzed intramolecular oxidative CO coupling of benzanilides. *Angew. Chem. Int. Edit.* **2008**, *47*, 6411–6413.

Ueda, S.; Nagasawa, H. Copper-catalyzed synthesis of benzoxazoles via a regioselective C–H functionalization/C–O bond formation under an air atmosphere. *J. Org. Chem.* **2009**, *74*, 4272–4277.

Yoshida, S.; Shiokawa, S.; Kawano, K.-I.; Ito, T.; Murakami, H.; Suzuki, H.; Sato, Y. Orally active benzoxazole derivative as 5-HT_3 receptor partial agonist for treatment of diarrhea-predominant irritable bowel syndrome. *J. Med. Chem.* **2005**, *48*, 7075–7079.