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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.

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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-HT₃ 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

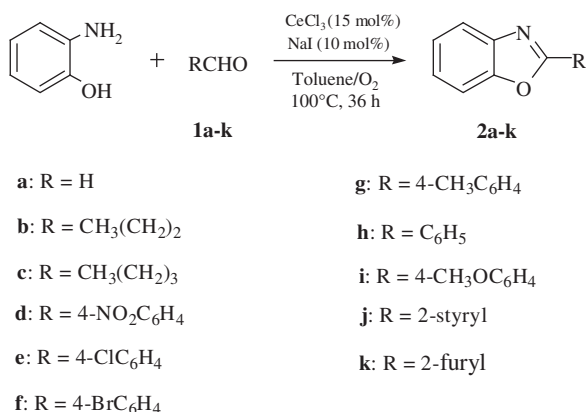
carboxylic acid derivatives in the presence of strong acid under harsh conditions (Pottorf et al., 2003). Another traditional method for the preparation of benzoxazoles includes the condensation of 2-aminophenols with aldehydes and subsequent oxidative cyclization of the imine intermediate (Osowska and 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



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 ($^\circ\text{C}$)	Yield (%) ^b
1	–	Toluene	100	<5
2	CuCl_2 (10)	Toluene	100	15
3	AlCl_3 (10)	Toluene	100	20
4	$\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (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.

^aReaction conditions: 2-aminophenol, 1.2 mmol; benzaldehyde, 1 mmol; solvent, 5 mL; 100°C for 36 h under O_2 .

^bGC-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 \times 0.32 mm \times 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 \times 0.25 mm \times 0.25 μm) column. Melting points were determined using a Yamato melting point apparatus Model MP-21 and are uncorrected. ^1H 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 ^1H 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 \times 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 $271\text{--}273^\circ\text{C}$ (Kidwai et al., 2006, yield 75%; mp $270\text{--}272^\circ\text{C}$).

2-(4-Chlorophenyl)benzoxazole (2e) Yield 80%; this compound was obtained as white crystals, mp $152\text{--}154^\circ\text{C}$ (Kawashita et al., 2003, yield 88%; mp $153\text{--}154^\circ\text{C}$).

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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