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Original article

Yttrium-catalyzed heterocyclic formation *via* aerobic oxygenation: A green approach to benzothiazoles

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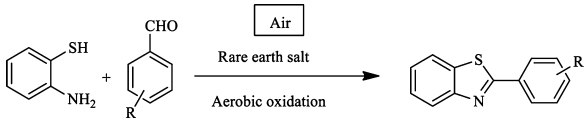
ABSTRACT

The YCl_3-catalyzed aerobic oxidative cyclization reaction for the synthesis of benzothiazoles has been developed. This method provides a practical, effective and green synthetic approach to benzothiazoles which are important units in many biologically active compounds.

1. Introduction

Oxidation reaction is one of the most important transformations in organic synthesis [1]. However, these reactions essentially involve the use of stoichiometric oxidants, leading to large amounts of waste that are not at all environmentally benign. An oxidation process with molecular oxygen or in air, is called aerobic oxygenation which addresses these issues in both economic and environmental ways [2]. Since air or pure oxygen is inexpensive while water is the only byproduct, aerobic oxygenations are comparatively greener and more preferable.

Benzothiazoles are common building blocks in many pharmaceuticals that exhibit remarkable biological and therapeutic activities. For example, benzothiazole derivatives have been used for diabetes [3], antitumor drugs [4] and amyloid inhibitors for treatment of Alzheimer's disease [5]. As a consequence, much effort has been devoted to the preparation of benzothiazoles. Several synthetic methodologies have been developed over the years. In the most cases, catalytic amounts of cyanide [6], metal oxide nanocrystals [7], chlorobenzene [8], copper (I) [9], and an excess of oxidants, such as $POCl_3$ [10], $K_2S_2O_8$ [11] and H_2O_2 [12,13] are required. They also suffer from some bottlenecks such as the use of toxic and expensive reagents or catalysts, long reaction time, harsh reaction conditions, side reactions and low yields. Far less is known, however, about aerobic oxidative cyclizations forming benzothiazoles. The development of an efficient and facile synthetic route to benzothiazoles in air is becoming increasingly timely.



Scheme 1. The process to benzothiazole derivatives.

Herein, we report the synthesis of benzothiazole derivatives *via* a reaction of o-aminothiophenol with various aldehydes catalyzed by yttrium chloride in air (Scheme 1). This methodology successfully combines C–H bond cleavage, dioxygen activation and oxidative C–N bond functionalization in terms of green chemistry and atom economy. We demonstrated that yttrium chloride plays a decisive role in aerobic oxidation.

2. Experimental

^1H NMR and ^{13}C NMR spectrums were made on Bruker ARX 400 for proton. Melting points were recorded on a WRS-2 data microscopic melting point apparatus and were uncorrected. Flash column chromatography was carried out using silica gel (200–300). All reagents were obtained from commercial sources and used as received.

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A general procedure for preparation of dihydropyrazines **3**: YCl_3 (0.0098 g, 0.05 mmol) were dissolved in 10 mL EtOH and stirred until the solid dissolved completely in refluxing, then 2-aminobenzenethiols **1a** (0.118 mL, 1.1 mmol) and benzaldehyde **2a** (0.101 mL, 1.0 mmol) was added into the reaction mixture. After 30 min, the reaction was complete monitored by TLC analysis. The reaction mixture was cooled to room temperature, and then evaporated in vacuum. The product purified by column chromatography (PE–EtOAc = 20:1) to give white solid **3a** (0.2092 g, 99%). Other products were synthesized through the same procedure. All ^1H NMR and ^{13}C NMR results were summarized in Supporting information. The configuration of compounds **3a**–**3o** was assigned by comparing ^1H NMR and ^{13}C NMR data with known compounds [14–26].

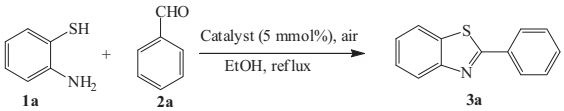
3. Results and discussion

Initially, 2-aminobenzenethiols (**1a**) and benzaldehyde (**2a**) were chosen as the model reactants to detect the reaction conditions. The screening of different parameters was summarized in Table 1. It turned out that in the absence of the catalysts, the product was obtained in only 17% yield (Table 1, entry 1). In the presence of traditional catalysts such as $CuCl_2$, $FeCl_3$ or $ZnCl_2$, the yields were dramatically improved (Table 1, entries 2–4). Interesting, the reaction appears to work more efficiently by using rare earth chlorides (Table 1, entries 5–7). Among the five selected catalysts, YCl_3 has been proved to be the most effective (Table 1, entry 6). Alcohol is the best solvent for catalyzed synthesis of **3a** in air.

Encouraged by the above experiments, we further explored the synthetic protocol and the scope by employing different kinds of aldehydes functionalized with electron-rich and electron-deficient groups. The results were summarized in Table 2. Clearly, all reactions worked well irrespective of the substituents on the aldehydes substrates (Table 2, entries 1–8). It is noteworthy that the reaction with aliphatic aldehyde (Table 2, entry 9) also afforded the desired product in satisfactory yield.

Nowadays development of novel method to synthesis antibacterial as well as antifungal agent is quite demanding and challenging for chemists and pharmacists. The present protocol has been applied to the synthesis of benzothiazoles **3j**, **3k**, **3l**, **3m** and **3n** (Table 3, entries 1–5) which identified as potent β-glucuronidase inhibitors [27] in satisfactory yield. Compound **3o** (Table 3, entry 6) which has strong antibacterial activity [28] was obtained in lower yield, because the reactant **2o** with strong electron donor can be oxidized much easier than other reactants.

Table 1
Catalyst-screen for the synthesis of **3a**[a]

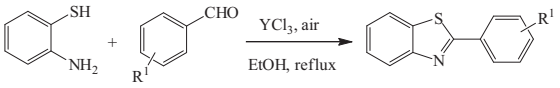


1a **2a** **3a**

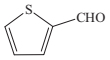
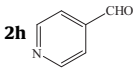
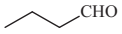
Entry	Catalyst	Time (h)	Yield (%)[b]
1	None	12	17
2	$CuCl_2$	6	78
3	$FeCl_3$	3	76
4	$ZnCl_2$	3	82
5	$LaCl_3$	3	81
6	YCl_3	3	99
7	$GdCl_3$	3	91

[a] 2-Aminobenzenethiol (1.1 equiv.), benzaldehyde (1.0 equiv.), catalyst (5 mol%).
[b] Isolated yield.

Table 2
YCl_3-catalyzed synthesis of benzothiazoles **3** from *o*-aminothiophenols **1a** and aldehydes **2**.[a]

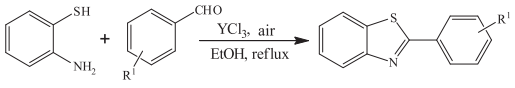


1a **2a-i** **3a-i**

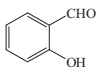
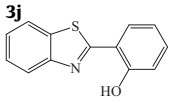
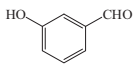
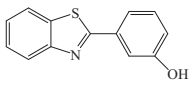
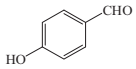
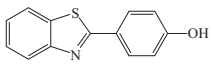
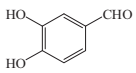
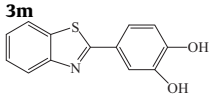
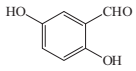
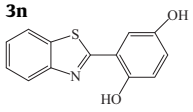
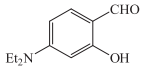
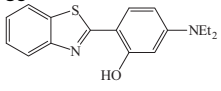
Entry	Aldehyde	Product	Yield (%)[b]
1	**2a** R^1=4-H	**3a**	99
2	**2b** R^1=4-F	**3b**	98
3	**2c** R^1=4-Cl	**3c**	95
4	**2d** R^1=4-CH_3	**3d**	81
5	**2e** R^1=4-OCH_3	**3e**	92
6	**2f** R^1=2-OMe	**3f**	90
7	**2g** 	**3g**	96
8	**2h** 	**3h**	97
9	**2i** 	**3i**	70

[a] Using *o*-aminothiophenol (1.1 equiv.), aldehyde (1.0 equiv.), YCl_3 (5 mol%) reflux in EtOH.
[b] Isolated yield.

Table 3
YCl_3-catalyzed synthesis of bioactive benzothiazoles **3**.[a]



1a **2j-n** **3j-n**

Entry	Aldehyde	Product	Yield (%)[b]
1	**2j** 	**3j** 	93
2	**2k** 	**3k** 	99
3	**2l** 	**3l** 	84
4	**2m** 	**3m** 	99
5	**2n** 	**3n** 	99
6	**2o** 	**3o** 	30[c]

[a] Using *o*-aminothiophenol (1.1 equiv.), aldehyde (1.0 equiv.), YCl_3 (5 mol%) reflux in EtOH.
[b] Isolated yield.
[c] Using 10 mol% of YCl_3.