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Cyanide as a powerful catalyst for facile synthesis of benzofused heteroaromatic compounds via aerobic oxidation

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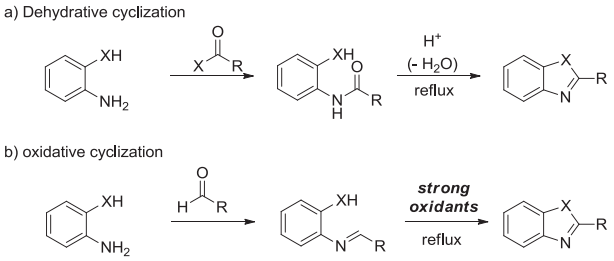
ABSTRACT

Highly efficient synthesis of benzofused heteroaromatic compounds via aerobic oxidation catalyzed by cyanide anion has been developed. The Schiff bases derived from 2-aminophenol and aldehydes provided the corresponding benzoxazoles in high yields in the presence of a catalytic amount of cyanide in an open flask under ambient conditions without the use of any external metal co-oxidants and bases. Furthermore, we have developed a catalytic sequential one-step protocol for the synthesis of benzoxazoles by adding a catalytic amount of NaCN to Schiff bases generated in situ from 2-aminophenol and aldehydes without the isolation of imine intermediates. This one-pot protocol was further extended to the synthesis of benzothiazoles from 2-aminothiophenol and aldehydes. A variety of aldehydes could be applied to this sequential one-pot protocol and the desired benzofused azole products were obtained in high yields.

1. Introduction

Benzofused heteroaromatic compounds, in particular benzofused azoles, are important building blocks in biologically and therapeutically active compounds, natural products, and functional materials.[1] Consequently, a number of methods have been developed for the synthesis of these important building blocks.[2–4] One of the conventional methods for the preparation of the benzofused heteroaromatic compounds involves the condensation of the corresponding aniline derivatives bearing nucleophilic moiety (XH in Scheme 1) at the *ortho*-position with carboxylic acids or their derivatives followed by cyclization reaction in the presence of strong acids at high temperature through dehydration (Scheme 1(a)).[5] Alternatively, these important building blocks are prepared via oxidative cyclization of Schiff bases derived from the corresponding *ortho*-substituted aniline derivatives with aldehydes in the presence of strong oxidants.[6–8] However, this method requires the use of stoichiometric or excess amounts of strong oxidants as compared to the respective Schiff base substrates (Scheme 1(b)).

Recently, aerobic oxidations employing oxygen as the ultimate oxidant have attracted much attention from the synthetic community.[9] In this regard, several examples of the synthesis of benzofused azole compounds via aerobic oxidations have been reported.[10–12] However, most aerobic oxidation protocols developed generally require toxic metal catalysts and/or excess quantities of bases under relatively harsh reaction conditions. Thus, the development of a more efficient method for the synthesis of benzofused heteroaromatic compounds via aerobic oxidation under mild conditions is highly desired.



Scheme 1. Conventional approaches for the synthesis of benzofused heteroazole compounds (X=O, S, and NH).

Recently, we have reported that a nucleophile could act as an efficient catalyst for the synthesis of benzofused heteroaromatic compounds through aerobic oxidation. For example, cyanide efficiently converted Schiff bases derived from *ortho*-aminophenol and aldehydes to the corresponding benzoxazoles in an open flask under ambient conditions without using any other metal salts and bases.[13,14] We have also developed a one-pot protocol for the synthesis of benzoxazoles from *ortho*-aminophenols and aldehydes in the presence of stoichiometric amount of cyanide without the isolation of imine intermediates. However, it was observed that the

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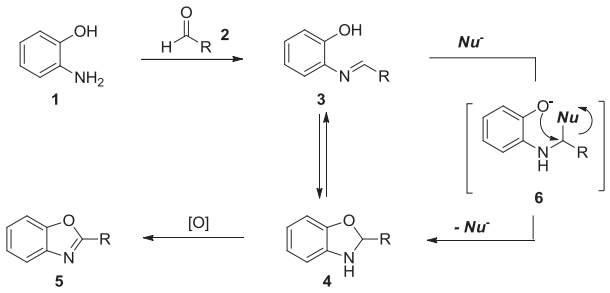
yields from the one-pot protocol were somewhat lower than those from the reactions with the corresponding imines due to benzoin reactions of the aldehydes in the presence of NaCN.[15] In addition, although the cyanide used for this transformation could be removed by a simple aqueous extraction, the need to use a stoichiometric amount of NaCN might lead the synthetic community to be reluctant to use this protocol. In order to overcome the lower yields from the one-pot protocol and stoichiometric use of NaCN, we have developed a more efficient synthetic protocol for the synthesis of benzoxazoles through the sequential addition of a catalytic amount of NaCN to Schiff bases generated in situ from aldehydes and *ortho*-aminophenols.

Herein we would like to report the development of highly efficient cyanide-catalyzed synthesis of benzoxazoles from the corresponding Schiff bases via aerobic oxidation. We also described the improved synthetic protocol for the catalytic one-pot synthesis of benzoxazoles through subsequent addition of a catalytic amount of NaCN to the Schiff bases generated from 2-aminophenols with aldehydes without the isolation of imine intermediates. This sequential one-pot method was further extended to the synthesis of benzothiazoles with 2-aminothiophenol.

2. Results and discussion

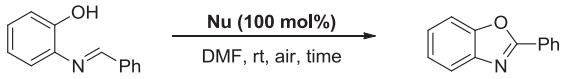
Although several methods for the synthesis of benzoxazoles via aerobic oxidation have been developed,[10] most of the aerobic oxidation methods require the use of metal catalysts and super-stoichiometric amounts of bases under relatively harsh reaction conditions. Thus, we first attempted to develop a method to prepare benzoxazoles from Schiff bases through the aerobic oxidative cyclization using air as a terminal oxidant under mild reaction conditions without any assistance of metal catalysts and/or bases. It is generally accepted that the formation of benzoxazole **5** from Schiff base **3** proceeds in a two-step sequence (Scheme 2).[6] The first step is an equilibrium step between Schiff base **3** and benzoxazoline intermediate **4**. Benzoxazoline **4** undergoes subsequent oxidation to afford benzoxazole **5**. We hypothesized that under aerobic oxidative cyclization of Schiff base **3**,[10] the first equilibrium step might be the rate determining step for the overall process. In this scenario, if the rate of the first step were accelerated, the overall reaction rate for the synthesis of benzoxazole could increase. One way to facilitate the rate of the first step might be addition of a nucleophile. A more reactive nucleophile could readily add to the imine in Schiff base **3** to afford intermediate **6**, which could more easily undergo a ring closing reaction to generate benzoxazoline **4** due to the better leaving ability of the nucleophile. Overall, the nucleophile was expected to decrease the activation energy for the first equilibrium step, which eventually facilitates the formation of benzoxazole **5**.



Scheme 2. Working hypothesis.

In order to test our working hypothesis, we commenced with our studies to find a suitable nucleophile to promote this transformation via aerobic oxidation under ambient conditions (Table 1).

Table 1
Screening of nucleophiles



3a 5a

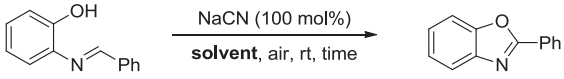
Entry	Nucleophile	Time (h)	Yield (%)[a]
1	—	96	N.R.[b]
2	NaCN	1	92
3	NaSPh	24	N.R.[b]
4	NaOPh	24	N.R.[b]
5	NaOAc	24	N.R.[b]
6	NaO*t*-Bu	24	N.R.[b]
7	DMAP	24	N.R.[b]
8	NEt_3	24	N.R.[b]
9	KCN	1	91
10[c]	NaCN	48	30

[a] Isolated yield.
[b] N.R. means no reaction.
[c] Under argon atmosphere.

To our delight, the addition of a nucleophile significantly facilitated the formation of benzoxazole; with a stoichiometric amount of NaCN the desired product **5a** was obtained in quantitative yield at room temperature in an open flask in 1 h (entry 2), whereas no oxidative cyclization reaction did proceed in the absence of a nucleophile even after 4 days (entry 1). We further examined the possibility of other metal salts and nitrogen-based nucleophiles as catalysts for this transformation (entries 3–8). Rather disappointingly, no nucleophiles other than cyanide could promote this oxidative cyclization reaction. The counter cation of cyanide displayed very little difference in the reactivity and KCN was also turned out to be effective in this transformation (entry 9). In order to confirm that air is the terminal oxidant, the same reaction was carried out under an argon atmosphere (entry 10). Under such conditions, benzoxazole **5a** was initially formed but no further conversion was observed thereafter. We believed that the formation of benzoxazole **5a** at the beginning of the reaction might be due to the oxidative cyclization of Schiff base **3a** with the oxygen dissolved in DMF and the oxidation reaction proceeded until the dissolved oxygen was completely consumed. Upon the complete consumption of the dissolved oxygen, however, no further formation of benzoxazole was observed. These results strongly supported that the air is the terminal oxidant in this transformation.

Next, other reaction parameters were optimized (Table 2). Interestingly, the choice of solvent had a significant effect on the

Table 2
Optimization of reaction conditions



3a 5a

Entry	Solvent	Time (h)	Yield (%)[a]
1	DMF	1	92
2	Dioxane	24	Trace
3	THF	24	Trace
4	EtOH	24	75
5	CH_3CN	24	70
6[b]	DMSO	1	92 (99)[c]
7[b,d]	DMSO	8	93 (99)[c]
8[b,e]	DMSO	48	90 (97)[c]
9[b,f]	DMSO	96	74 (90)[c]

[a] Isolated yield.
[b] DMSO-d_6 was used.
[c] The yields in parentheses were determined by ^{1}H NMR analysis of the crude mixture.
[d] 10 mol % of NaCN was used.
[e] 5 mol % of NaCN was used.
[f] 1 mol % of NaCN was used.