Synthesis of 2-aryl benzoxazoles from aldoximes

Abstract

Wide spectrum of biological activities of benzoxazole heterocycles aroused great interest for the development of newer methods for their synthesis. We herein report a copper catalyzed method for the synthesis of 2-aryl benzoxazoles from the reaction of aldoxime and 2-iodobromobenzene as the ligand. The reaction proceeds with the copper-catalyzed dehydration of aldoxime leading to the nitilium ion which might be undergoing hydrolysis and subsequent C-O bond formation in one-pot to afford 2-aryl benzoxazoles. The pure products were isolated and characterized by ‘H NMR, and 13C NMR data.

Keywords: benzoxazoles, aldoxime, 2-iodo bromobenzene, copper catalysis, dmeda

Introduction

Benzoxazoles are a class of important scaffolds and possess a wide range of applications in pharmaceutical research (Figure 1). Particularly, 2-substituted benzoxazole derivatives have remarkable biological potential including anticancer, antitumour and inhibitory activities. Furthermore, this motif is also abundant in several functional materials such as engineering plastics, optical brightener for textiles and metal sensors. As a result, there are increasing demands to devise versatile methods for the construction of 2-substituted benzoxazoles.

The condensation of 2-aminophenol and carboxylic acid or its surrogates such as aldehydes, acid chlorides, orthoesters, and β-oxodithioesters under various reaction conditions are the straight forward approaches to construct the benzoxazole unit. However, these methods are often associated with several limitations such as the use of highly toxic reagents, strong acids and, in some cases, harsh reaction conditions. Therefore, development of suitable process for the construction of benzoxazole unit is demanding. Consequently, use of transition-metal catalyzed route offers a mild and reliable protocol to achieve the benzoxazole system with enhanced efficiency. Among the transition-metal catalyzed routes are considered as an ideal choice because of their commercially viability, less expensive and low cytotoxicity. Moreover, copper catalyzed benzoxazole synthesis relies on either intramolecular O-arylation or direct coupling of 1,2-dihalo benzene with primary amide or nitrile (Figure 2). For instance, Evindar & Batey reported the CuI/1,10-Phen catalyzed cyclization of ortho-haloanilides to 2-aryl benzoxazoles. Punniamurthy et al. used CuO-nanoparticle for intramolecular annihilation of ortho-bromoanilide under ligand free condition to afford 2-aryl benzoxazoles. In another report, Xie et al. annulated the N-(2-iodo-bromo-phenyl) benzamides, and even the less reactive N-(2-chlorophenyl) benzamides, via Cu-catalyzed intramolecular coupling to 2-aryl benzoxazoles reactions using methyl 2-methoxybenzoate as the ligand under mild reaction conditions. Similar protocol for the synthesis of benzoxazoles in aqueous medium was reported by Sammartin et al. Copper-catalyzed cross-coupling of 1,2-dihaloanilenes with primary amide leading to the initial formation of ortho-halo anilide and subsequent cyclization to 2-aryl benzoxazole was reported by Batey and co-workers. Copper-catalyzed reaction of aryl halides with nitriles leading to N-arylazides and benzoxazoles has been developed by Xi et al. Very recently, Dong et al. synthesized benzoxazole frameworks from the reaction of phenols and primary amines in the presence of NH4PF6 over copper under mild conditions using O2 as the terminal oxidant. Cu-catalyzed cyclization reactions of 2-aminophenols with β-diketones in the presence of Bromsted acid was also reported.

In continuation of our earlier work on copper-catalyzed N-aryl amide synthesis from aldoximes, here, we report a ligand assisted copper-catalyzed protocol for the synthesis of 2-aryl benzoxazoles from the reaction of aldoxime and 1-bromo-2-iodobenzene.

Figure 1: Some examples of biologically potent benzoxazoles.
Materials and methods

All melting points are uncorrected. All reactions were carried out in oven dried round bottom flask. Solvents and reagents were used as such without further purification. The reactions were monitored by TLC and the residue was purified by column chromatography on silica gel (Rankem, India, mesh size 60-120), using an ethyl acetate-petroleum ether (60-80°C) mixture as eluent. Yield of the reactions were calculated with respect to 1, 2-dihalo benzene. All NMR spectra were recorded on Bruker Avance III (400MHz for 1H NMR, 100MHz for 13C NMR) spectrometers; chemical shifts were expressed in δ units relative to TMS signal as internal reference in CDCl₃ and DMSO-d₆.

The coupling constants (J values) are expressed in Hz.

General procedure for the synthesis of benzoxazole (3a-i)

To a mixture of 1-bromo-2-iodobenzene (100mg, 0.354mmol) and aldoxime (1.416mmol) in o-xylene (1ml), K₂CO₃ (1.062mmol) and DMEDA (0.106mmol) was added and the mixture was heated at 140°C for 16h. After completion of the reaction, it was diluted with dichloromethane and water. The organic layer was separated and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate and petroleum ether mixture as the eluent to get the pure product (3a-i).

Results and discussion

In our earlier report, we have described a ligand-assisted copper-catalyzed protocol for the regioselective synthesis of N-aryl amide from the reaction of aldoxime and aryl iodide. We have proposed that in the presence of the copper catalyst, aldoxime undergo dehydration leading to intermittent nitrilium ion which subsequently passed through reductive elimination and nucleophilic attack of water or another equivalent of aldoxime to produce N-aryl amides. Here, we speculated that, the presence of an additional halo group to the aromatic ring might induce a further reactive site for copper catalyzed C-O bond formation to afford 2-aryl benzoxazoles (3).

At the onset, we started our investigation by the treatment of benzaldoxime 1a and 1,2-diiodobenzene (2) as the substrates to carrying out the reaction in o-xylene in the presence of 10mol% CuSO₄.5H₂O, K₂CO₃ (5 equiv), DMEDA (30mol%) at 130°C for 12h. However, to our dismay, under this reaction condition no desired benzoxazole was produced, rather the benzaldoxime (1a) was transformed in to a mixture of benzamida and o-iodo benzinilide in 42% and 36% yield respectively. By changing to other metal catalyst like CuO, copper powder, CuFe₂O₄, CuCl in both polar and non-polar solvents did not afford 3a rather the oxime was converted to benzonitrile. However, instead of diiode benzene, when 1-bromo-2-iodobenzene (2) was treated with aldoxime in the presence of CuI (10mol%), K₂CO₃ (3 equiv), dimethyl ethylenediamine (DMEDA) (30 mol %) in 1 ml of o-xylene, 2-phenyl benzoxazole was produced in 52% yield (Table 1) (Entry 1). Replacing CuI catalyst by CuSO₄.5H₂O lesser amount (34-44%) of 3a was produced (Entries 6 & 7). Other copper catalyst including copper ferrite, copper oxide and copper chloride are less effective (Entries 5,9 & 10). Moreover, in the absence of ligand o-bromo benzinilide was formed (<15%) (Entry 2). Changing the solvent to polar solvents like DMF, DMSO did not produce 3a (Entries 3 & 4). When DMEDA was used as both ligand and base 34% of 3a was isolated (Entry 6). Among the tested bases (i.e. K₂CO₃, KOH, Cs₂CO₃ and AcONa) K₂CO₃ (3 equiv) affords the best result. It may be noted here that lowering the reaction temperature to 100°C did not produce 3a even after a period of 36h.

After having established the optimum reaction conditions, we next explored the substrate scope of the CuI-catalyzed annulation reaction (Table 1). In general, different substituents such as Me, OMe, Cl, NMe₂, on the aromatic ring of aldoxime were well tolerated to the reaction condition and provided the corresponding 2-aryl benzoxazoles in appreciable yield (Table 2). Unfortunately, electron-with drawing substituent i.e. NO₂ group to the aldoxime did not produce the required benzoxazole.
Table 1 Optimization of the reaction condition[a]

| Entry | Catalyst | Base | Ligand | Solvent | Yield (%) |
|-------|----------|------|--------|---------|-----------|
| 1     | Cul      | K$_2$CO$_3$ | DMEDA  | o-xylene | 52        |
| 2     | Cul      | K$_2$CO$_3$ | ----    | o-xylene | 0         |
| 3     | Cul      | K$_2$CO$_3$ | DMEDA  | DMF     | 0         |
| 4     | Cul      | K$_2$CO$_3$ | DMEDA  | DMSO    | 0         |
| 5     | CuFe$_3$O$_4$ | K$_2$CO$_3$ | ----    | o-xylene | <5        |
| 6     | CuSO$_4$·5H$_2$O | DMEDA | DMEDA | o-xylene | 34        |
| 7     | CuSO$_4$·5H$_2$O | K$_2$CO$_3$ | DMEDA | o-xylene | 44        |
| 8     | Cul      | AcONa   | DMEDA  | o-xylene | 20        |
| 9     | CuCl     | K$_2$CO$_3$ | DMEDA  | DMF     | 5         |
| 10    | CuO      | K$_2$CO$_3$ | DMEDA  | o-xylene | 22        |
| 11    | Cul      | KOH     | 1,10-Phen | o-xylene: H$_2$O (3: 1) | 40        |
| 12    | Cul      | KOH+ Cs$_2$CO$_3$ (1.5 equiv each) | DMEDA | H$_2$O (8 equiv) | 0         |
| 13    | Cul      | Cs$_2$CO$_3$ | 1,10-Phen | o-xylene | 47        |

[a]Reaction condition: 1-bromo-2-iodobenzene (2) (100mg, 0.354mmol), benzaldoxime (1a) (1.416mmol), base (1.062mmol), ligand (0.106mmol, 30mol%), solvent (1ml), 140°C, 16h.

Table 2 Synthesis of 2-aryl benzoxazoles from 1-bromo-2-iodobenzene[b]

| Entry | Aldoxime | Benozxazole | Yield (%) |
|-------|----------|-------------|-----------|
| 1     | 1a       | 3a          | 52        |
| 2     | 1b       | 3b          | 46        |
Table Continued...

| Entry | Aldoxime | Benoxazole | Yield (%) |
|-------|----------|------------|-----------|
| 3     | \( \text{H}_3\text{C} - \text{C}_6\text{H}_4\text{N} = \text{N} - \text{O} \text{H} \) (1c) | \( \text{O} - \text{N} - \text{H} - \text{C}_6\text{H}_4\text{CH}_3 \) (3c) | 54         |
| 4     | \( \text{Cl} - \text{C}_6\text{H}_4\text{N} = \text{N} - \text{O} \text{H} \) (1d) | \( \text{O} - \text{N} - \text{H} - \text{C}_6\text{H}_4\text{Cl} \) (3d) | 48         |
| 5     | \( \text{MeO} - \text{C}_6\text{H}_4\text{N} = \text{N} - \text{O} \text{H} \) (1e) | \( \text{O} - \text{N} - \text{H} - \text{C}_6\text{H}_4\text{OMe} \) (3e) | 51         |
| 6     | \( \text{MeO} - \text{MeO} - \text{C}_6\text{H}_4\text{N} = \text{N} - \text{O} \text{H} \) (1f) | \( \text{O} - \text{N} - \text{H} - \text{C}_6\text{H}_4\text{OMe} \) (3f) | 50         |
| 7     | \( \text{MeO} - \text{MeO} - \text{MeO} - \text{C}_6\text{H}_4\text{N} = \text{N} - \text{O} \text{H} \) (1g) | \( \text{O} - \text{N} - \text{H} - \text{C}_6\text{H}_4\text{OMe} \) (3g) | 53         |
| 8     | \( \text{F} - \text{C}_6\text{H}_4\text{N} = \text{N} - \text{O} \text{H} \) (1h) | \( \text{O} - \text{N} - \text{H} - \text{C}_6\text{H}_4\text{OMe} \) (3h) | 43         |
| 9     | \( \text{N} - \text{N} - \text{C}_6\text{H}_4\text{N} = \text{N} - \text{O} \text{H} \) (1i) | \( \text{O} - \text{N} - \text{H} - \text{C}_6\text{H}_4\text{OMe} \) (3i) | 38         |

\( \text{H} \) NMR (400MHz, CDCl\(_3\)) \( \delta \): 2H, 7.83 - 7.77 (m, 1H), 7.64 - 7.58 (m, 1H), 7.58 - 7.51 (m, 3H), 7.38 (dd, 2H, J\(_1\)=6Hz, J\(_2\)=3.2Hz); \( \text{C} \) NMR (100MHz, CDCl\(_3\)) \( \delta \): 163.0, 150.7, 142.1, 131.5, 128.9, 127.6, 125.1, 124.5, 120.0, 110.6.

**Conclusion**

In conclusion, we have demonstrated an oxidative facial one-pot strategy for the synthesis of 2-arylbenzoxazoles in moderate yield. This reaction proceeds by using less expensive CuI-catalyst for the transformation of aryl aldoxime to 2-aryl benzoxazoles in the presence of 1-bromo-2-iodobenzene.

**Summary of spectroscopic data**

i. 2-phenyl benzo[d] oxazole\(^5\) (3a): Yellowish crystalline solid; m. p. 100-102\(^\circ\)C. \( \text{H} \) NMR (400MHz, CDCl\(_3\)) \( \delta \): 8.32 - 8.25 (m, 2H), 7.83 - 7.77 (m, 1H), 7.64 - 7.58 (m, 1H), 7.58 - 7.51 (m, 3H), 7.38 (dd, 2H, J\(_1\)=6Hz, J\(_2\)=3.2Hz); \( \text{C} \) NMR (100MHz, CDCl\(_3\)) \( \delta \): 163.0, 150.7, 142.1, 131.5, 128.9, 127.6, 125.1, 124.5, 120.0, 110.6.

ii. 2-(2-chlorophenyl) benzo [d] oxazole\(^5\) (3b): White crystalline solid; m. p. 63-65\(^\circ\)C. \( \text{H} \) NMR (400MHz, CDCl\(_3\)) \( \delta \): 8.16 (dd, 1H, J\(_1\)=7.2Hz, J\(_2\)=1.8Hz), 7.91-7.84 (m, 1H), 7.67-7.55 (m, 2H), 7.51-7.36 (m, 4H); \( \text{C} \) NMR (100MHz, CDCl\(_3\)) \( \delta \): 160.9, 150.5, 141.6, 133.4, 131.9, 131.8, 131.4, 126.9, 125.6, 124.6, 120.5, 110.7.

iii. 2-(p-tolyl) benzo [d] oxazole\(^5\) (3c): Yellowish white crystalline solid; m. p. 100-102\(^\circ\)C. \( \text{H} \) NMR (400MHz, CDCl\(_3\)) \( \delta \): 8.32 - 8.25 (m, 2H), 7.83 - 7.77 (m, 1H), 7.64 - 7.58 (m, 1H), 7.58 - 7.51 (m, 3H), 7.38 (dd, 2H, J\(_1\)=6Hz, J\(_2\)=3.2Hz); \( \text{C} \) NMR (100MHz, CDCl\(_3\)) \( \delta \): 163.0, 150.7, 142.1, 131.5, 128.9, 127.6, 125.1, 124.5, 120.0, 110.6.

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solid; m. p. 88-90°C. 1H NMR (400MHz, CDCl3): δ 88.16 (d, 2H, J=3.48Hz), 7.81-7.75 (m, 1H), 7.61-7.53 (m, 1H), 7.40-7.30 (m, 4H), 2.44 (s, 3H); 1C NMR (100MHz, CDCl3): δ 161.3, 150.6, 142.1, 142.0, 129.6, 127.5, 124.8, 124.3, 119.8, 110.5, 21.6.

iv. 2-(4-chlorophenyl) benzo[d] oxazole32 (3d): White crystalline solid; m. p. 144-145°C. 1H NMR (400MHz, CDCl3): δ 8.21 (d, 2H, J=9.2Hz), 7.79-7.72 (m, 1H), 7.60-7.53 (m, 1H), 7.39-7.29 (m, 2H), 7.04 (d, 2H, J=8.8Hz), 3.90 (s, 3H); 1C NMR (100MHz, CDCl3): δ 162.0, 150.7, 141.9, 137.7, 129.3, 128.8, 125.6, 125.3, 124.7, 120.0, 110.6.

v. 2-(4-methoxyphenyl) benzo[d] oxazole33 (3e): Yellowish white crystalline solid; m. p. 126 -128°C. 1H NMR (400MHz, CDCl3): δ 8.21 (d, 2H, J=9.2Hz), 7.79-7.72 (m, 1H), 7.60-7.53 (m, 1H), 7.39-7.29 (m, 2H), 7.04 (d, 2H, J=8.8Hz), 3.90 (s, 3H); 1C NMR (100MHz, CDCl3): δ 163.5, 150.6, 142.1, 142.0, 129.6, 127.5, 124.8, 124.5, 124.3, 119.8, 110.5, 110.3, 51.5.

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Conflict of interest

The author declares no conflict of interest.

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