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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 using N,N'-dimethyl ethylenediamine (DMEDA) 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 ^{1}H NMR, and ^{13}C NMR data.

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

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Dinesh Kumar Nayak, Niranjan Panda
Department of Chemistry, National Institute of Technology Rourkela, India

Correspondence: Niranjan Panda, Department of Chemistry, National Institute of Technology Rourkela, Odisha, India-769008, Tel +9166 1246 2653, Email niranjanpanda@gmail.com, npanda@nitrkl.ac.in

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Introduction

Benzoxazoles are a class of important scaffolds and possess a wide range of applications in pharmaceutical research[1] (Figure 1). Particularly, 2-substituted benzoxazole derivatives have remarkable biological potential including anticancer, antitumour and inhibitory activities.[2–7] Furthermore, this motif is also abundant in several functional materials such as engineering plastics, optical brightener for textiles and metal sensors.[8–16] 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[17] or its surrogates such as aldehydes,[18–21] acid chlorides,[22–24] orthoesters,[25–27] and β-oxodithioesters[28] 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.[29] 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 employed transition-metal catalysts,[30–41] copper-catalyzed routes are considered as an ideal choice because of their commercially viability, less expensive and low cytotoxicity.[42–50] Moreover, copper catalyzed benzoxazole synthesis relies on either intramolecular O-arylation of 2-halobenzanilides[42–45] or direct coupling of 1,2-dihalo benzene with primary amide[46] or nitrile[47,48] (Figure 2). For instance, Evindar & Batey[42] reported the CuI/1,10-Phen catalyzed cyclization of ortho-haloanilides to 2-aryl benzoxazoles. Punniamurthy et al.[43] used CuO-nanoparticle for intramolecular annulation of ortho-bromoanilide under ligand free condition to afford 2-aryl benzoxazoles. In another report, Xie et al.[44] 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 Sanmartin et al.[45] Copper-catalyzed cross-coupling of 1,2-dihaloarenes 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.[46] Copper-catalyzed reaction of aryl halides with nitriles leading to N-arylamides and benzoxazoles has been developed by Xiang et al.[47,48] Very recently, Dong et al. synthesized benzoxazole frameworks from the reaction of phenols and primary amines in the presence of NH_4PF_6 over copper under mild conditions using O_2 as the terminal oxidant.[49] CuI-catalyzed cyclization reactions of 2-aminophenols with β- diketones in the presence of Brønsted acid was also reported.[50]

In continuation of our earlier work on copper-catalyzed N-aryl amide synthesis from aldoximes,[51] 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.

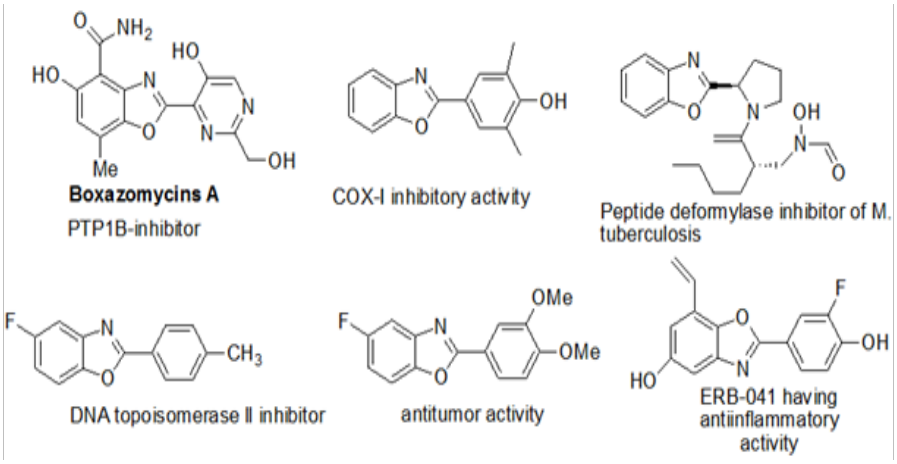

Figure 1 Some examples of biologically potent benzoxazoles.

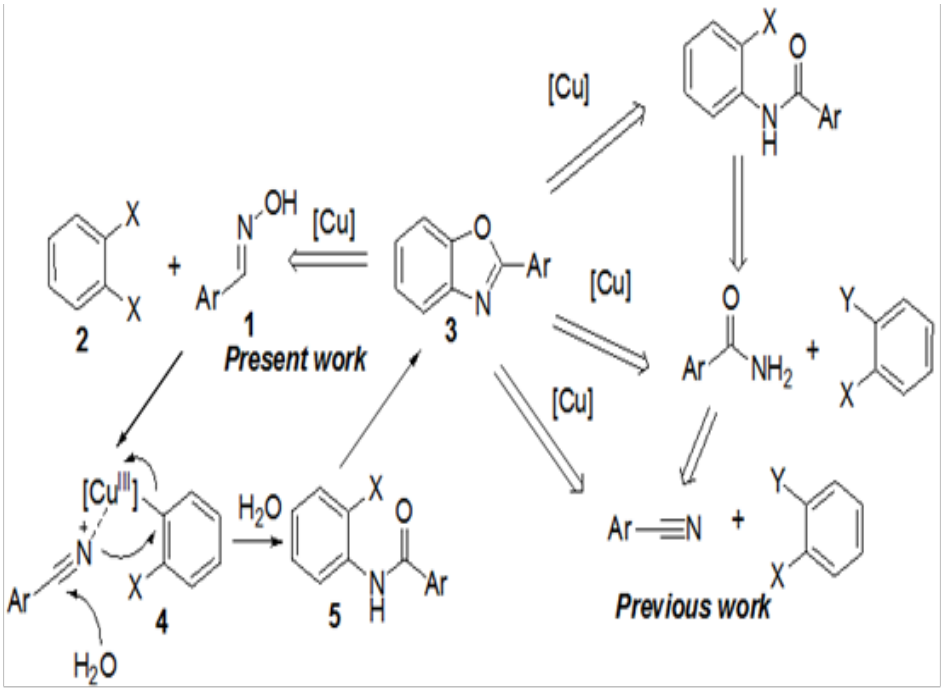

Figure 2 Copper-catalyzed 2-aryl benzoxazole synthesis.

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, mess 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 ^{1}H NMR, 100MHz for ^{13}C NMR) spectrometers; chemical shifts were expressed in δ units relative to TMS signal as internal reference in $CDCl_3$ and DMSO-d_6. 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), K_2CO_3 (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 Na_2SO_4 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% $CuSO_4.5H_2O$, K_2CO_3 (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, $CuFe_2O_4$, CuCl in both polar and non-polar solvents did not afford **3a** rather the oxime was converted to benznitrile. However, instead of diiode benzene, when 1-bromo-2-iodobenzene **(2)** was treated with aldoxime in the presence of CuI (10mol%), K_2CO_3 (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 $CuSO_4.5H_2O$ 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. K_2CO_3, KOH, Cs_2CO_3 and AcONa) K_2CO_3 (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, NMe_2, 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. NO_2 group to the aldoxime did not produce the required benzoxazole.

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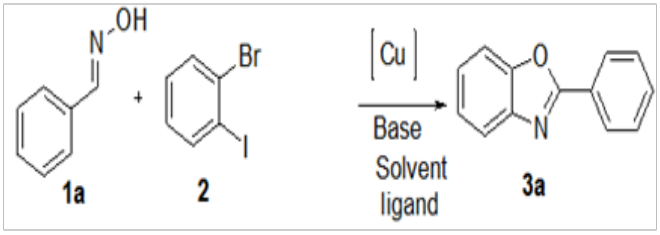
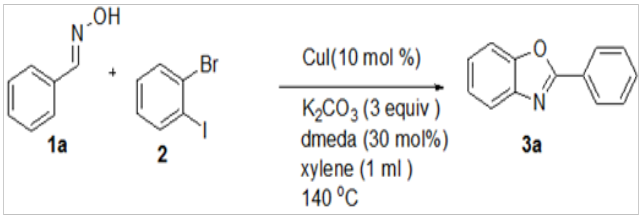
Table 1 Optimization of the reaction condition[a]



Entry	Catalyst	Base	Ligand	Solvent	Yield (%)
1	CuI	K_2CO_3	DMEDA	o-xylene	52
2	CuI	K_2CO_3	-----	o-xylene	0
3	CuI	K_2CO_3	DMEDA	DMF	0
4	CuI	K_2CO_3	DMEDA	DMSO	0
5	$CuFe_2O_4$	K_2CO_3	----	o-xylene	<5
6	$CuSO_4.5H_2O$	DMEDA	DMEDA	o-xylene	34
7	$CuSO_4.5H_2O$	K_2CO_3	DMEDA	o-xylene	44
8	CuI	AcONa	DMEDA	DMF	5
9	CuCl	K_2CO_3	DMEDA	o-xylene	20
10	CuO	K_2CO_3	DMEDA	o-xylene	22
11	CuI	KOH	1,10-Phen	o-xylene: H_2O (3: 1)	40
12	CuI	KOH+ Cs_2CO_3 (1.5 equiv each)	DMEDA	H_2O (8 equiv)	0
13	CuI	Cs_2CO_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 [a]



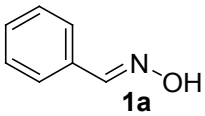
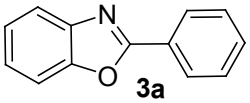
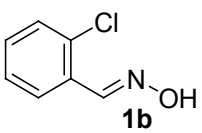
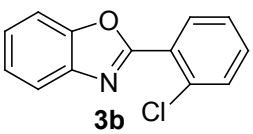
Entry	Aldoxime	Benzoxazole	Yield (%)
1			52
2			46

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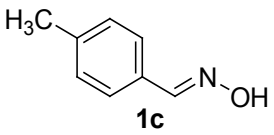
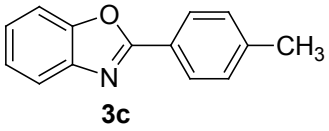
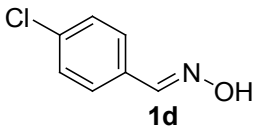
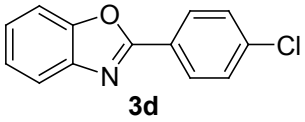
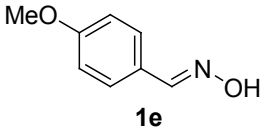
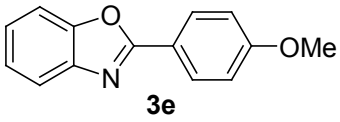
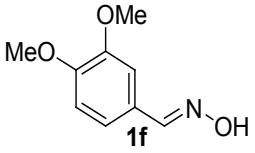
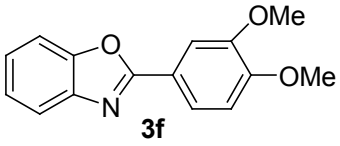
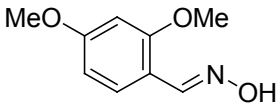
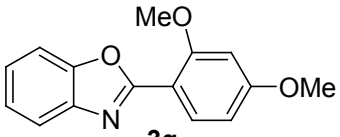
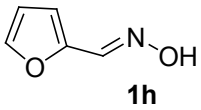
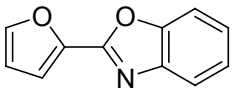
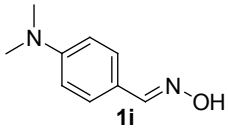
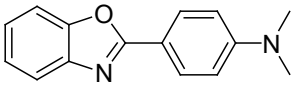
Table Continued..

Entry	Aldoxime	Benzoxazole	Yield (%)
3	 **1c**	 **3c**	54
4	 **1d**	 **3d**	48
5	 **1e**	 **3e**	51
6	 **1f**	 **3f**	50
7	 **1g**	 **3g**	53
8	 **1h**	 **3h**	43
9	 **1i**	 **3i**	38

[a]Reaction condition; 1-Bromo-2-iodobenzene (**2**) (100mg, 0.354mmol), aldoxime (1.416mmol), CuI (0.0354mmol), K_2CO_3 (1.062mmol), DMEDA (0.106mmol), o-xylene (1ml), 140°C, 16h.

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[52] (3a):** Yellowish crystalline solid; m. p. 100-102°C. ^{1}H NMR (400MHz, $CDCl_3$) δ8.32 - 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); ^{13}C NMR (100MHz, $CDCl_3$) δ163.0, 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[53] (3b):** White crystalline solid; m. p. 63-65°C. ^{1}H NMR (400MHz, $CDCl_3$) δ8.16 (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); ^{13}C NMR (100MHz, $CDCl_3$) δ160.9, 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[53] (3c):** Yellowish white crystalline

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solid; m. p. 88-90°C. ^{1}H NMR (400MHz, $CDCl_3$): δ8.16 (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): ^{13}C NMR (100MHz, $CDCl_3$): δ163.3, 150.6, 142.1, 142.0, 129.6, 127.5, 124.8, 124.5, 124.3, 119.8, 110.5, 21.6.

iv. **2-(4-chlorophenyl) benzo [d] oxazole[52] (3d):** White crystalline solid; m. p. 144-145°C. ^{1}H NMR (400MHz, $CDCl_3$): δ8.21 (d, 2H, J=8.4Hz), 7.82-7.76 (m, 1H), 7.63-7.57 (m, 1H), 7.52 (d, 2H, J=8.8Hz), 7.42-7.26 (m, 2H) :^{13}C NMR (100MHz, $CDCl_3$): δ162.0, 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] oxazole[52] (3e):** White crystalline solid; m. p. 126 -128°C. ^{1}H NMR (400MHz, $CDCl_3$): 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): ^{13}C NMR (100MHz, $CDCl_3$): δ163.1, 162.3, 160.6, 142.2, 129.3, 124.6, 124.4, 119.6, 119.6, 114.3, 110.3, 55.4.

vi. **2-(3,4-dimethoxyphenyl) benzo[d] oxazole[54] (3f):** White crystalline solid; m. p. 109-110°C. ^{1}H NMR (400MHz, $CDCl_3$) δ7.88 (dd, 1H, J_1=8.4Hz, J_2=Hz), 7.80-7.53 (m, 2H), 7.61-7.55 (m, 1H), 7.38-7.32 (m, 2H), 7.01 (d, 1H, J=8.4Hz), 4.04 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 163.1, 151.9, 150.7, 149.2, 142.2, 124.7, 124.5, 121.2, 119.6, 111.0, 110.4, 110.0, 56.1, 56.0.

vii. **2-(2,4-dimethoxyphenyl) benzo[d] oxazole[55] (3g):** Yellowish white crystalline solid; m. p. 58-60°C. ^{1}H NMR (400MHz, $CDCl_3$) δ8.11 (d, 1H, J=8.4Hz), 7.84-7.75 (m, 1H), 7.59-7.52 (m, 1H), 7.36-7.26 (m, 2H), 6.66-6.58 (m, 2H), 4.01 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ163.5, 161.6, 159.9, 150.0, 142.2, 132.4, 124.4, 124.1, 119.8, 110.2, 109.0, 105.2, 99.1, 56.1, 55.6.

viii. **2-(furan-2-yl) benzo[d] oxazole[52] (3h):** Yellowish white crystalline solid; m. p. 107-108 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ7.81- 7.74 (m, 1H), 7.69 (d, 1H, J=8Hz), 7.61- 7.55 (m, 1H), 7.41- 7.34 (m, 2H), 7.32-7.26 (m, 1H), 6.67-6.61 (m, 1H); ^{13}C NMR (100MHz, $CDCl_3$): δ155.4, 150.1, 145.7, 142.6, 141.6, 125.3, 124.8, 120.1, 114.2, 112.2, 110.6.

ix. **4-(benzo[d]oxazol-2-yl)-N,N-dimethylaniline[52] (3i):** White crystalline solid; m. p. 185-187 °C .^{1}H NMR (400MHz, $CDCl_3$): δ8.13 (dd, 2H, J_1=7.2Hz, J_2=2Hz), 7.72 (dd, 1H, J_1=6.8Hz, J_2=1.6Hz), 7.57-7.51 (m, 1H), 7.36-7.24 (m, 2H), 6.81-6.74 (m, 2H), 3.07 (s, 6H); ^{13}C NMR (100MHz, $CDCl_3$): 164.2, 152.3, 150.5, 142.5, 129.0, 124.1, 123.9, 119.0, 114.1, 111.5, 110.1, 40.1.

Acknowledgements

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Conflict of interest

The author declares no conflict of interest.

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