Rapid synthesis of benzoxazole (intramolecular C-O bond formation), an efficient two step protocol: Role of bases and solvent

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Received: 23.02.2019 ***Accepted: 22.03.2019*** ***Published Online 15.04.2019***

Abstract

An efficient, rapid synthesis of benzoxazole in two steps (1) base catalyzed synthesis of the haloanilide from haloaniline and acyl chloride (2) metal catalyzed, ligand assisted intramolecular C-O bond formation leading to benzoxazole synthesis. Inexpensive, solvents, bases and shorter reaction times of this protocol make this method superior to all reported methods for the synthesis of benzoxazole.

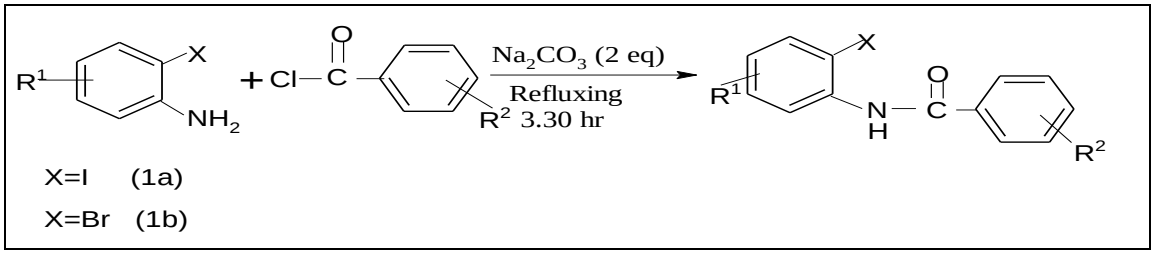
Keywords: Benzoxazole, Haloanilide, Intramolecular c-o bond formation, cyclization.

Introduction:

Benz-fused azoles are an important class of molecules found in a variety of natural products[1] and are important target in drug discovery[2] oxazole have been indicated as 5-HT_3 receptor partial agonist[3], HIV reverse transcriptase inhibitor L-697-661[4], COX inhibitors[5], estrogen receptor β agonist ERB-041[6], thrombin inhibitors[7], R_2 antagonist 5-HT uptake inhibitors[8], and inhibition of the human cytomegalovirus protease[9]. 2-arylbenzoxazole possess the important biaryl pharmacophore and exhibit a variety of biological activities, including antimicrobial[10], antiviral[11], and antitumor properties[12], for example a 2-arylbenzoxazole AJ 19561 was recently isolated as a cytotoxic metabolite from the extract of streptomyces[13], other applications of benzoxazole includes herbicides, such as fenoxaprop and fluorescent whitening agent dyes such as bis- benzoxazole ethylene and arene [14].

There are two general strategies for synthesizing 2-arylbenzoxazole based on substrate 2-aminophenol as starting materials. One is condensation of 2-aminophenol with carboxylic acid derivatives in the presence of strong acids at high temperature , the other is via photochemical, oxidative and radical cyclization of phenolic Schiff bases derived from the condensation of 2-aminophenol and aldehydes [15]. For oxidative cyclization, various oxidants such as $BaMnO_4$[16], $Pb(OAc)_4$[17], NiO_2[18], $ThClO_4$[19], $Mn(OAc)_3$[20], DDQ[21], I_2[22] , hydrotalcite[23] ,and molecular sieve[24] have been used. However most of these oxidants are not economic or environmentally benign also the starting material 2-aminophenol is not easily accessible. Alternative approaches employing 2-haloaniline have been reported by Evindar and coworkers who have synthesised benzoxazole using 2-haloaniline as precursors. Acylation of 2-haloaniline could generate *o*- haloanilide substrate required for the copper catalyzed cyclization[25.] Barbero and coworkers reported copper catalyzed intramolecular *O*-arylation of aryl bromide and aryl chloride[26.] Viirre and coworkers reported copper catalyzed domino annulations approaches to the synthesis of benzoxazoles under mirowave-accelerated and conventional thermal conditions; this reaction

was carried out under pressure[27]. Bonnamour and co workers have described iron catalyzed intramolecular *O*-arylation of haloanilides[28] and an iron-catalyzed domino C–N/C–O cross-coupling reaction to produce benzoxazole[29]. These reactions suffers drawback i.e. took long reaction time (20-24 hrs) for each steps, and uses expensive solvents. The use of anhydrous ferric chloride and DMF also limits the use due to hygroscopic nature of ferric chloride and difficulty in the separation of DMF. In the present communication the synthesis of benzoxazole through an intramolecular C-O bond formation is reported to complete in short reaction time with excellent yield. The two steps process involves (1) 2-haloanilide formation using 2-haloaniline and acyl chloride in 3.30 hrs, using base as a catalyst, (2) intramolecular C-O bond formation using copper catalyzed cyclization of haloanilide to generate benzoxazoles in 7 hrs as shown in scheme 1. The first step uses Na_2CO_3 as base and CH_2Cl_2 as solvent. The second step uses CS_2CO_3 as base and toluene as solvent in presence of CuI as catalyst and TMHD as ligand. The present method reduced reaction time from 40-48 hrs to 10.30 hrs (3.30 +7.0).

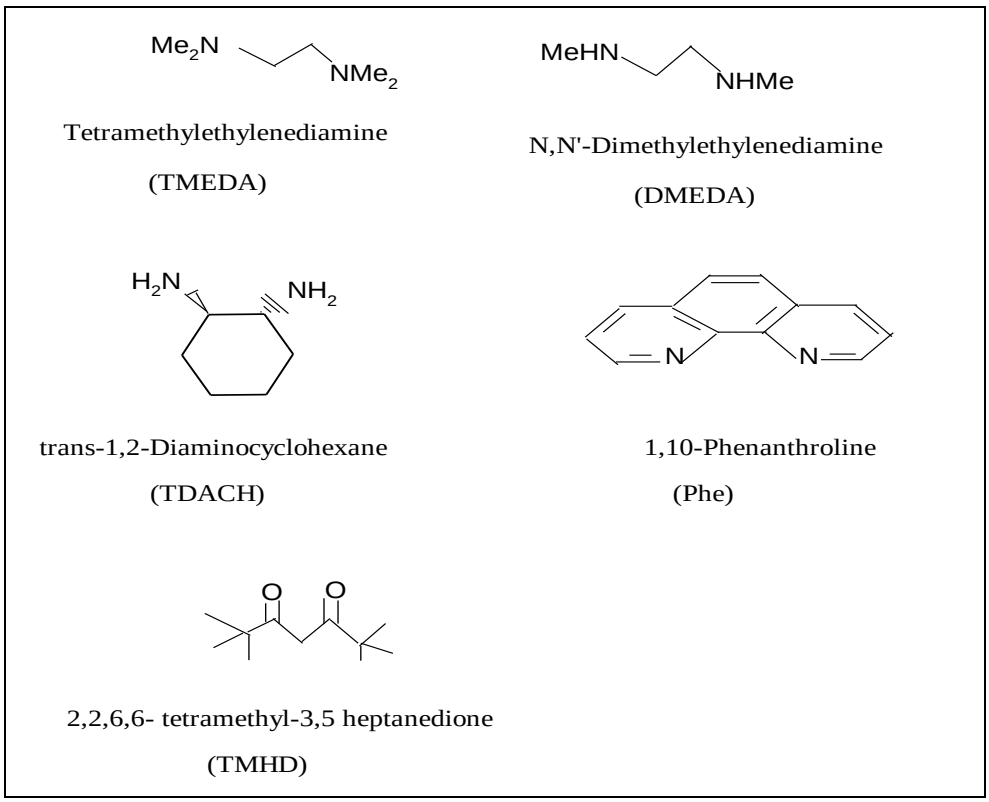


1 **2**

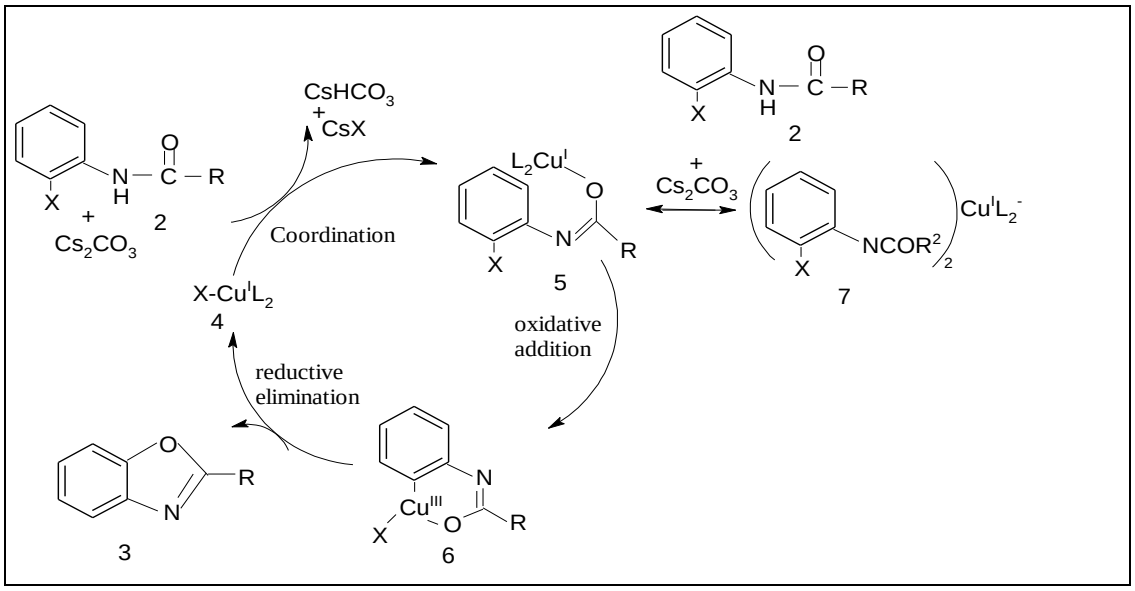
Scheme 1

2 **3**

Scheme 2



Scheme 3



Scheme 4 Mechanistic proposal for the copper-catalyzed formation of benzoxazole 3

Experimental:

Unless otherwise specified, all the reagents were purchased from Sigma- Aldrich, Himedia and were used without further purification. Common organic solvents were purchased from Rankem. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates. IR spectra were recorded by Shimadzu FT-IR spectrometer in KBr palates (γ_{max} in $cm^{-1)}$. ^1H NMR spectra were recorded by Bruker Avance II-400 and Jeol AL 300 FTNMR spectrometer. ^{13}C NMR spectra were recorded at 400 MHz. Chemical shifts (δ) are givin in ppm relative to TMS. Mass spectra (ESI-MS) were obtained by Agitent 6310 ion trap spectrometer.

Procedure

(a) General procedure for prepration of haloanilide 2 from ortho-haloaniline and acyl chloride:

To a solution of ortho-haloaniline (0.5mmol, 1.0 equiv) in CH_2Cl_2 (5ml) Na_2CO_3 (1.0 mmol, 2 equiv) and benzoyl chloride (0.60mmol , 1.2equiv) were added. The reaction mixture was refluxed for 3.30 hrs. Then cooled at room temperature and diluted with EtOAc (20 ml). The organic layer washed with (2×15 ml) water, dried over $MgSO_4$ and the solvent was removed in vacuo. The product was carried to next step without further purification.

(b) General procedure for preparation of benzoxazole (3):-

To a mixture of the iodo (or some case bromo) amide precursors 2 (0.64 mmol), CuI (0.0095g, 0.05mmol, 0.078 equiv), TMHD (0.10mmol, 0.15 equiv) and Cs_2CO_3 (2.0 mmol, 3.12 equiv), was added in toluene (10ml) at room temperature under a nitrogen atmosphere. The contents were refluxed and monitored by TLC then allowed to cool to room temperature. The reaction mixture was then diluted with EtOAc (20 ml) and washed with H_2O (2×10 ml) and brine (1×15 ml). The organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The crude product was recrystalized from ethanol.

Spectral and analtytical data of 2-haloanilides

N-(2-iodophenyl) benzamide (2a) [25]. Mp 135-137°C; ESI-MS (m/z) = 324 (M+1); IR (KBR): υ (cm^{-1}) – 3215, 1649, 1573, 1516, 1465, 748, 489; ^1H-NMR (300 MHz, $CDCl_3$), ***δ*** = 8.45-8.48 (dd, 1H, J= 8.4 Hz, NH), 8.29 (br s, 1H), 7.96-7.98 (d, 2H, J = 6.9 Hz), 7.81-7.83 (d, 1H, J = 8.1 Hz,), 7.50-7.61 (m, 3H), 7.38-7.43(td, 1H, J = 15 Hz,) 6.86-6.91 (td, 1H, J = 15 Hz,).

N-(2-iodophenyl)-4-methoxy benzamide (2b) [25]. Mp 152-153 °C; ESI-MS (m/z) = 354 (M+1); IR (KBR): υ (cm^{-1}) – 3265, 2839, 1645, 1521, 1504, 1431,750, 513; ^1H-NMR (400 MHz, $CDCl_3$), ***δ*** = 8.34-8.37 (dd, 1H, J = 1.52 Hz, J= 1.48 Hz,), 8.144(br s, 1H), 7.83-7.87 (m, 2H), 7.70-7.73(dd, 1H, J = 1.44 Hz, J = 1.4 Hz,), 7.28-7.32(td, 1H, J = 15.56 Hz,), 6.90-6.94 (m, 2H), 6.75-6.80 (td, 1H, J= 16.84 Hz,), 3.78-3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz) ***δ*** 164.8, 162.7, 138.7, 138.4, 132.8, 129.4, 129.1, 125.8, 121.6, 114.1, 90.1, 55.5.

N - (2-iodophenyl)-4-nitro benzamide (2c) Mp 140-144; ESI-MS (m/z) = 367 (M-1); ^1H-NMR (400 MHz, $CDCl_3$), ***δ*** = 8.35-8.38 (d, 3H, J = 8.76 Hz), 8.30 (br s, 1H), 8.11-8.13 (d, 2H, J = 8.72 Hz), 7.82-7.84 (d, 1H, J = 9.24 Hz), 7.40-7.44 (td, 1H, J = 15.56 Hz,), 6.91-6.96 (td, 1H, J = 16.8 Hz).

N-(2-iodophenyl)-3, 4-dimethoxy benzamide (2d) Mp 154-157 °C; ESI-MS (m/z) = 384 (M+1); IR (KBR): υ (cm^{-1}) – 3263, 2839, 1643, 1583, 1514, 1465, 758, 557; ^1H-NMR (400 MHz, $CDCl_3$), ***δ*** = 8.35-8.37 (dd, 1H, J = 1.48 Hz, J= 1.56), 8.18 (br s, 1H), 7.72-7.74 (dd, 1H, J = 1.44 Hz, J= 1.4 Hz), 7.44-7.49 (m, 2H), 7.30-7.34 (td, 1H, J = 16.96 Hz), 6.87-6.89 (d, 1H, J = 8.32 Hz), 6.77-6.81(td, 1H, J = 16.88 Hz), 3.89 (s, 3H), 3.88 (s, 3H).

N-(4-fluoro, 2-bromophenyl) benzamide (2e)[25]. Mp 140-142 °C; ESI-MS (m/z) = 295 (M+1); ^{1}H-NMR (400 MHz, $CDCl_3$), ***δ*** = 8.48-8.51(dd, 1H, J = 5.56 Hz, J = 5.56 Hz), 8.33 (br s, 1H), 7.91-7.94(m, 2H), 7.57-7.61(m, 1H), 7.50-7.54 (m, 2H), 7.32-7.35 (dd, 1H, J = 2.92 Hz, J = 2.92 Hz), 7.08-7.13 (m, 1H).
N-(2-bromo-4-fluorophenyl)-4-methoxy benzamide (2f) Mp 154-156 °C; ESI-MS (m/z) = 324 (M+1); IR (KBR): υ (cm^{-1}) – 3271, 2839, 1643, 1525, 1506, 1481, 1253, 763, 615; ^{1}H-NMR (400 MHz, $CDCl_3$), 1H), ***δ*** = 8.39-8.42 (dd, 1H, 1H, J = 5.6 Hz, J = 5.6 Hz), 8.17 (br s, 1H), 7.79-7.83 (m, 2H), 7.23-7.26 (dd, 1H, J = 2.84 Hz, J = 2.88 Hz), 6.99-7.04 (m, 1H), 6.90-6.94 (m, 2H), 3.80 (s, 3H).

Spectral and analtytical data of 2-substituted phenyl benzoxazole

2-Phenyl benzoxazole (3a)[25]. Mp 98-101 °C; ESI-MS (m/z) = 196 (M+1); IR (KBR): υ (cm^{-1}) – 3059, 1614, 1475, 1448, 1342, 1051,744; ^{1}H-NMR (300 MHz, $CDCl_3$), ***δ*** = 8.24-8.27 (d, 2H, J = 7.5 Hz), 7.76-7.79 (dd, 1H, J = 3.3 Hz, J = 3 Hz), 7.52-7.60 (m, 4H), 7.34-7.37(m, 2H).
2-(4-methoxy phenyl) benzoxazole (3b)[25]. Mp 97-98°C; ESI-MS (m/z) = 226 (M+1); IR (KBR): υ (cm^{-1}) – 3051, 2843, 1604, 1504, 1454, 1346, 1018,740; ^{1}H-NMR (400 MHz, $CDCl_3$), ***δ*** = 8.11-8.13 (m, 2H), 7.65-7.67 (m-1H), 7.46-7.49 (m, 1H), 7.23-7.26 (m, 2H), 6.94-6.96 (m, 2H), 3.81 (s, 3H). ^{13} C NMR ($CDCl_3$, 400 MHz) ***δ*** 163.7, 162.1, 149.5, 141.0, 128.3, 125.6, 124.7, 120.5, 118.5, 113.3, 109.3, 54.4.
2-(3, 4-dimethoxy phenyl)benzoxazole (3c)[26]. Mp 109-112 °C; ESI-MS (m/z) = 256 (M+1); ^{1}H-NMR (400 MHz, $CDCl_3$), ***δ*** =7.77-7.80(d, 1H, J = 1.96 Hz), 7.66-7.69 (m, 2H), 7.47-7.50 (m, 1H), 7.23-.28 (m, 2H), 6.90-6.92(d, 1H, J= 8.08 Hz), 3.94 (s, 3H), 3.89 (s, 3H).
2-(4-nitro phenyl) benzoxazole (3d) [30]. Mp 263-265°C; ESI-MS (m/z) = 240.4 (M+1); ^{1}H-NMR (400 MHz, $CDCl_3$), ***δ*** = 8.43-8.46 (m, 2H), 8.38-8.41 (m, 2H), 7.82-7.84 (m,1H), 7.63-7.65 (m,1H), 7.40-7.47 (m, 2H).
6-fluoro, 2-phenyl benzoxazole (3e) [26]. Mp 110-111°C; ESI-MS (m/z) = 212 (M-1); ^{1}H-NMR (400 MHz, $CDCl_3$), ***δ*** =8.18-8.24(m, 2H), 7.62-7.71(dd, 1H, J = 4.88 Hz, J = 4.96 Hz),7.49-7.56 (m, 3H), 7.29-7.32 (dd, 1H, J = 2.36 Hz, J = 2.4Hz), 7.07-7.14 (td, 1H, J =20.8 Hz).
6-Fluoro-2-(4-methoxy phenyl) benzoxazole (3f). Mp 160 °C; ESI-MS (m/z) = 244 (M+1); ^{1}H-NMR (400 MHz, $CDCl_3$), ***δ*** =8.04-8.06 (d, 2H, J = 8.44 Hz), 7.53-7.57(m, 1H), 7.17-7.19 (d, 1H, J = 5.88 Hz), 6.91-7.0 (m, 3H), 3.79 (s, 3H).

Results and Discussion:

The methodology involves the synthesis of haloanilides using 2-iodoaniline (1) and benzoyl chloride as a model substrate. The reaction conditions were optimized using different baseas, catalysts, solvents and reaction time (table 1). The effect of various bases viz K_2CO_3, Na_2CO_3, $LiCO_3$, Cs_2CO_3, K_3PO_4 and organic base pyridine was studied in CH_2Cl_2. Good conversion of haloaniline to anilide (2) was observed with Na_2CO_3 and K_2CO_3, with Na_2CO_3 being superior with 98% yield. Encouraged by this result we further examined this reaction with different solvents using Na_2CO_3 as the base. CH_2Cl_2 proved to be the best solvent among an array of solvent tested (table-1, entry-2). Reaction time increases when reaction was performed at room temperature. In solvent free condition the yield got decreased (table 1, entry 11). After determining the optimizing conditions (1.0 equiv of haloaniline precursor, 1.2 equiv of acyl chloride, 2.0 equiv of Na_2CO_3 in CH_2Cl_2 were refluxed for 3.30 hrs (scheme 1). Substituted acyl chloride and haloaniline provided the desired haloanilide **2a-2f** in excellent yield (85-99%) (Table 2, entry 1-7). Both electron donating and electron withdrawing groups gave excellent results. There are no signaificant effect electron donating and withdrawing groups on anilide formation.

In second step for C-O bond formation haloanilide **(2)** was chosen and reagent combination of CuI, TMHD, Cs_2CO_3 and toluene was tested (table 3, entry 1). To our delight, haloanilide **(2)** cyclized rapidly at reflux for 7 hrs to give benzoxazole **(3)** in 97% yield (scheme 2). Another set of experiments revealed the crucial role of solvent and base. Thus use of Cs_2CO_3 led to the best results and other bases such as K_3PO_4 and K_2CO_3 (table 3, entry 7, 8) took longer time in furnishing the target benzoxazole **(3).** The use of other bases Na_2CO_3 and $LiCO_3$ (table 3, entry 9, 10) did not led to the desired conversion. The use of solvent other than toluene such as dioxane (table 3, entry 2) resulted in lower yield. The use of CH_2Cl_2 : toluene mixture led slow reaction (20 hrs) with excellent yield. The use of hexane, dichloromethane (table 3, entry 3, 4) led to very low conversion. The use of acetonitrile: toluene mixture (table 3, entry 6) led to 65% cyclized product. These results suggest that nonpolar solvent toluene is the best choice with Cs_2CO_3 as the best base.

The role of ligands and catalysts on intramoleular cyclization was studied (table 4), the table shows that copper metal, CuI and $CuCl_2$ produced acceptable results for the cyclization of haloanilide. The air stable inexpensive CuI gave the best results. Consequently, CuI was chosen as catalyst precursor for subsequent experiments although it is conceivable that other metal compounds could be used with comparable or greater success. Other metals such as manganese chloride, manganese acetate, molybdic acid, ammonium metavanadate (table 4, entry 6-9) gave anilide and slight conversion of cyclized product. Nickel nitrate (table 4, entry 10) took longer time and gave lower yield. It is interesting to note that copper compounds in various oxidation states are catalytically active and presumably are transformed to the same active catalyst under the reaction condition [27]. Various ligands studied are given in scheme-3 (table 4, scheme 3). TMHD provided the best results for the synthesis of benzoxazole **(3)** starting from both 2-iodoanilides and 2-bromoanilides. DMEDA, and CHDA also gave superior results but TMEDA showed no conversion of substrate. 1, 10-phenanthroline (phe) which has been reported by Evindar et al was tried and formed that is also acts as efficient ligand under the present base and DME solvent system.

To explore the scope of the optimized reaction conditions, we decided to apply such protocol and slight modification of it to the C-O bond formation with a series of 2-haloanilide derivatives, (table 5), and scheme 4. As shown in table 5, the present methodology proved to be efficient for the synthesis of a number of benzoxazole **(3)** in excellent yields. Both 2-iodo and 2-bromoanilides afforded excellent results (table 5 entry 1) which are known to be the most active coupling partners for copper catalyzed arylation reaction. Moreover, the electronic nature of the aromatic substituent directly linked to the carbonyl moiety affect the reaction outcome. The presence of electron donating substituent's (table 5, entry 2, 3) accelerated the rate of the reaction giving product in shorter reaction time; whereas electron withdrawing group (table 5, entry 4) retarded the reaction.

A proposed mechanism for the intramolecular C-O bond formation of anilide to benzoxazole derivatives was shown in sheme 4. This transformation presumably occurred through a coordination of the amide function group of anilide to the Cu (I) center followed by an intramolecular oxidative addition of aryl halide to Cu (I), affording an intermediate complex 3. The resulting complex reacted with base to form Cu-O bond afforded an intermediate complex 4, which proceed the formation of the coupling product 2 and generation of the catalytic copper species (path A scheme 5). Various studies, have shown that copper in its different oxidation state (Cu (bronze), Cu^{I}, or Cu^{II}) are catalytically active, presumably a result of their conversion in to the same active species under the reaction conditions[31]. However, an alternative pathway via nucleophilic substitution in the first step [32] then followed by oxidative addition could not be completely ruled out (path B).

Table 1: Effect of base and solvent on anilide formation

Entry	X	Base	Solvent	Time(hr)	Temperature(^oC)	Yield(%)[a]
1	I	Li_2CO_3	CH_2Cl_2	4	refluxing	95
2	I	Na_2CO_3	CH_2Cl_2	3.30	Refluxing	98
3	I	Na_2CO_3	CH_2Cl_2	10	25^oC	99
4	I	Na_2CO_3	MeCN	4	refluxing	97
5	I	Cs_2CO_3	CH_2Cl_2	4.30	Refluxing	55
6	I	K_3PO_4	CH_2Cl_2	3.30	Refluxing	83
7	I	K_2CO_3	CH_2Cl_2	4.30	Refluxing	98
8	I	K_2CO_3	$C_6H_5CH_3$	21	Refluxing	*Nf*
9	I	C_5H_5N	$C_6H_5CH_3$	6	Refluxing	*Nf*
10	I	C_5H_5N	CH_2Cl_2	10	Refluxing	*Nf*
11	I	Na_2CO_3	-	3.30	55^oC	73

Reaction condition: 2-iodoaniline (0.5 mmol), benzoyl chloride (0.60 mmol), base (2 equiv.).
[a]isolated yield ; *Nf:* not formed

Table 2: Effect of substituents in haloaniline and acyl chloride on the synthesis of haloanilide

Entry	X	R^1	R^2	Product	Yield (%)[a]
1	I	-	-	2a	98,99[b]
2	I	-	4-OMe	2b	95
3	I	-	4-NO_2	2c	94
4	I	-	3, 4 di- OMe	2d	85
5	Br	4-F	Ph	2e	99
6	Br	4-F	4-OMe	2f	99

Reaction condition: 2-haloaniline (0.5 mmol), acyl chloride (0.6 mmol), Na_2CO_3 (2 equiv), CH_2Cl_2 (5ml), refluxed.
[a]isolated yield ; [b]yield obtained from the corresponding bromo precursor.

Table 3: Effect of bases and solvent on C-O bond formation (cyclization)

Entry	Solvent	Base	Time(hr)	Yield (%)	
				a	b
1	Toluene	Cs_2CO_3	7	97	-
2	1,4 di-oxane	Cs_2CO_3	7	81	-
3	Hexane	Cs_2CO_3	19	18	80
4	CH_2Cl_2	Cs_2CO_3	40	11	87
5	CH_2Cl_2 +Toluene	Cs_2CO_3	20	95	-
6	MeCN + Toluene	Cs_2CO_3	23	65	30
7	Toluene	K_3PO_4	17	80	-
8	Toluene	K_2CO_3	20	95	-
9	Toluene	Na_2CO_3	22	-	100
10	Toluene	Li_2CO_3	20	-	100

Reaction condition: N (2-halophenyl) benzamide (0.64mmol), CuI(0.05mmol), TMHD (0.10mmol), Cs_2CO_3(2 mmol) .
[a] isolated yield of cyclized product ; [b]isolated yield of corresponding anilide

Table 4: Influence of the nature of the catalyst and ligand in the intramolecular cyclization of 2-iodoanilide to give benzoxazole 3.

Entry	Metal catalysts	Ligand	Time(hr)	Yield (%)	
				a	b
1	CuI	TMHD	7	97	-
2	$CuCl_2.2H_2O$	TMHD	20	78	-
3	$CuSO_4.5H_2O$	TMHD	22	82	-
4	Cu metal powder	TMHD	27	77	-
5	$Cu(CH_3COO)_2.H_2O$	TMHD	9	81	-
6	$MnCl_2$	TMHD	24	8	86
7	$Mn(CH_3COO).4H_2O$	TMHD	24	12	82
8	$MoO_3.H_2O$	TMHD	9	8	88
9	NH_4VO_3	TMHD	20	10	87
10	$NiNO_3.6H_2O$	TMHD	17	83	-
11	CuI	TMEDA	18	-	100
12	CuI	DMEDA	18	87	-
13	CuI	Phe	7	97	-
14	CuI	TDACH	20	94	-

Reaction condition: N-(2-iodophenyl) benzamide (0.64mmol), CuI (0.05mmol), 1,10-phenanthroline (0.10mmol), Cs_2CO_3 (2 mmol).
[a]isolated yield of cyclized product. ; [b]isolated yield of corresponding anilide.

Table 5: Effect of substituents at R^1 and R^2 during cyclization

Entry	X	R^1	R^2	Time(hr)	Product	Yield(%)[a]
1	I	-	-	7	3a	97, 96[b]
2	I	-	4-OMe	7	3b	97
3	I	-	3,4-di-OMe	7	3c	82
4	I	-	4-NO_2	24	3d	91
5	Br	4-F		13	3e	86
6	Br	4-F	4-OMe	13	3f	82

Reaction condition: N (2-halophenyl) benzamide (0.64mmol), CuI (0.05mmol), TMHD (0.10mmol), Cs_2CO_3 (2 mmol).
[a]isolated yield. ; [b]yield obtained from the corresponding bromo precursor.

Conclusions:

In conclusion, we have described a simple, general and efficient rapid synthesis of benzoxazole, the best results are realized by using inexpensive and air stable copper (I) iodide and TMHD. Two steps were involve in the reaction process (1) 2-haloaniline reacted with acyl chloride to afford benzamide (2) intramolecular C-O bond formation of haloanilide resulted in the expected benzoxazoles synthesis. High efficiency and good substrate generality are displayed in this transformation under mild reaction condition. We believe that this method provides excellent complement to existing and newly reported benzoxazole synthesis methodology due to the easy accessibility of starting materials.

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