Copper-catalyzed one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones from 2-(*o*-haloaryloxy)acyl chlorides and primary amines

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Abstract

A facile and efficient Cu(I)-catalyzed one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-one derivatives has been developed. The condensation between 2-(*o*-haloaryloxy)acyl chlorides and primary amines followed by Cu(I)-catalyzed intramolecular C-N bond coupling afforded a variety of 2*H*-1,4-benzoxazin-3-(4*H*)-ones in good to excellent yields. Diversified substitutents on the 4-position could be conveniently introduced.

Keywords: Copper-catalyzed, one-pot; C-N coupling, condensation, 2*H*-1,4-benzoxazin-3-(4*H*)-one

Introduction

The 2*H*-1,4-benzoxazin-3-(4*H*)-one scaffolds can be found in many natural and synthetic bioactive compounds including potent pharmaceuticals, herbicides, and fungicides (Figure 1).[1-2] For example, several pyridazinylbenzoxazines (**A**) possess cardiotonic properties.[2a] A series of benzoxazinone derivatives (**B**) were found to be SGLT2 inhibitors.[2e] Some 7-amino-4-aryl benzoxazin-3-ones (**C**) can be employed as mineralocoricoid receptor-modulating agents.[2d] 4*H*-Benzo[1,4]oxazin-3-ones (**D**) are useful for the treatment of diabetes mellitus and the related obesity.[2b]

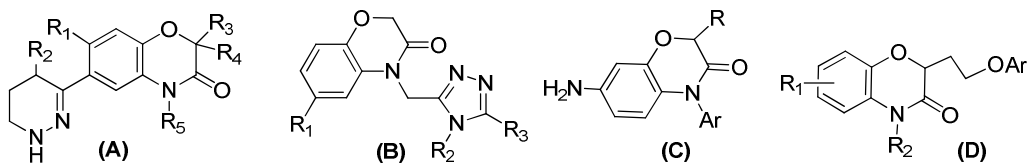
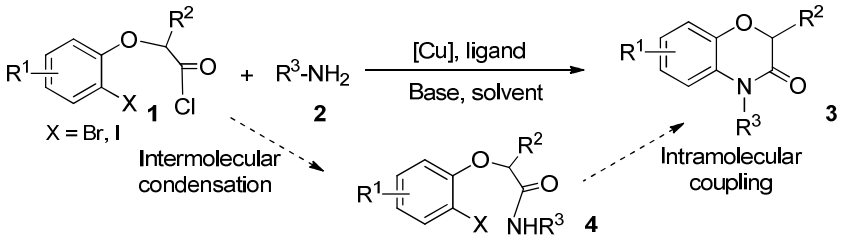


Figure 1. Structures of several biologically and pharmaceutically valuable 2*H*-1,4-benzoxazin-3-(4*H*)-one derivatives.

Common synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-one derivatives utilized stepwise procedures,[3] and these methods might suffer from tedious procedures, harsh conditions, and/or poor precursor scopes. Comparing with the traditional stepwise methods, one-pot protocols are highly efficient for the assembly of target products from simple starting materials, and could not only simplify the procedures, but also reduce the amount of pollutant emission. It was reported that 2*H*-1,4-benzoxazin-3-(4*H*)-ones could be synthesized by microwave-assisted one-pot reaction *via* Smiles rearrangment.[4] However, the high reaction temperature (150 ^{o}C) and narrow scope might make it less attractive. Rencently, it was found that substituted benzoxazinones were assembled *via* Pd-catalyzed intramolecular C-O bond formation,[5] but expensive Pd-catalyst was used and the substrate *N*-(2-bromophenyl)-2-hydroxyl amide should be prepared in advance.

In the last decade, copper-catalyzed coupling has drawn much attention for their high efficiency and low cost.[6] And during the past few years, Cu-catalyzed coupling reactions have been applied for the one-pot assembly of various heterocyclic compounds.[7-9] It was recently reported that 2*H*-1,4-benzoxazin-3-(4*H*)-ones could be efficiently synthesized *via* Cu(I)-catalyzed reactions between 2-halophenols and 2-haloacetamides.[10] The strategies are quite promising. However, the starting materials 2-halo amides[11] have to be prepared, and should be further purified by chromatography prior to use. Therefore, the development of an alternative and simple procedure with wider applications is still in demand. Herein, we wish to report a convenient, inexpensive and efficient copper-catalyzed one-pot protocol to assemble various 2*H*-1,4-benzoxazin-3-(4*H*)-ones from 2-(*o*-haloaryloxy)acyl chlorides and primary amines.

We envisaged that readily available *o*-halo α-aryloxyacyl chloride **1**[12] could react with primary amine **2** to give the corresponding amide **4** as the intermediate; and the latter would undergo an intramolecular C-N coupling process to afford 2*H*-1,4-benzoxazin-3-(4*H*)-one **3** under proper Cu-catalysis (Scheme 1).



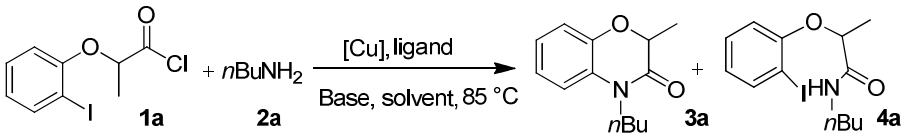
Scheme 1. The proposed one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones *via* Cu-catalyzed condensation/coupling process.

Results and Discussion

In our preliminary studies, 2-(*o*-iodophenoxy)acyl chloride **1a** and aliphatic primary amine **2a** were employed as the model substrates. The first attempt was performed in 1,2-dimethoxyethane (DME) with CuI (10 mol%) as the catalyst and 1,10-phenanthroline (1,10-Phen, 20 mol%) as the

ligand in the presence of K_2CO_3 at 85 °C (Table 1, entry 1). Both the desired product **3a** and the intermediate **4a** were obtained (21% and 45% yield, respectively), demonstrating that the reaction occurred in the desired manner. Considering that the poor yield of **3a** might result from the incomplete conversion in the intramolecular coupling process, we then attempted to optimize the reaction conditions. Both K_2CO_3 and K_3PO_4 gave low yields (entries 1 and 2). And Cs_2CO_3 was proven to be the most effective base (entry 3). Dioxane was superior to other solvents (DME, CH_3CN, and toluene) (entries 3-6). Different Cu(I)-catalysts such as CuI, CuBr and Cu_2O were also tested, and CuI acted as the best catalyst (entries 6-8). Among the ligands examined (1,10-Phen, 2,2'-bipyridine, DMEDA, and L-proline), 1,10-Phen was found to be the optimal (entries 6 and 9-11). In the absence of the ligand, the desired product was obtained only in 33% yield (entry 12). To our delight, the yield remained almost the same upon reducing the amount of CuI to 5 mol% (entry 13); while further reducing the amount would lead to a much lower yield (entry 14). Therefore 5 mol% of CuI in combination with 10 mol% of 1,10-Phen were chosen as the suitable promoters for this cascade reaction.

Table 1. Optimization of the reaction conditions[a]

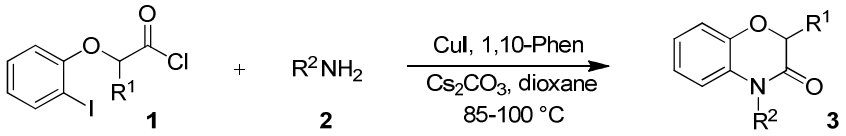


Entry	[Cu]	Ligand	Base	Solvent	Yield of **3a** (%)[b]
1	CuI	1,10-Phen	K_2CO_3	DME	21
2	CuI	1,10-Phen	K_3PO_4	DME	15
3	CuI	1,10-Phen	Cs_2CO_3	DME	76
4	CuI	1,10-Phen	Cs_2CO_3	MeCN	62
5	CuI	1,10-Phen	Cs_2CO_3	toluene	12
6	CuI	1,10-Phen	Cs_2CO_3	dioxane	96
7	CuBr	1,10-Phen	Cs_2CO_3	dioxane	71
8	Cu_2O	1,10-Phen	Cs_2CO_3	dioxane	32
9	CuI	2,2'-Bipy	Cs_2CO_3	dioxane	42
10	CuI	DMEDA	Cs_2CO_3	dioxane	49
11	CuI	L-Proline	Cs_2CO_3	dioxane	20
12	CuI	-	Cs_2CO_3	dioxane	33
13	CuI	1,10-Phen	Cs_2CO_3	dioxane	95[c]
14	CuI	1,10-Phen	Cs_2CO_3	dioxane	78[d]

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (0.55 mmol), Cu(I)-catalyst (0.05 mmol, 10 mol%), ligand (0.10 mmol, 20 mol%), and base (1.2 mmol, 2.4 equiv) in solvent (2 mL) under N_2 at 85 °C for 24 h. [b]Isolated yield. [c]CuI (5 mol%)/1,10-Phen (10 mol%) as the promoters. [d]CuI (2.5 mol%)/1,10-Phen (5 mol%) as the promoters.

After the optimized conditions were established, we then investigated the scope of this Cu(I)-catalyzed cascade reaction by employing a variety of 2-(*o*-iodophenoxy)acyl chlorides[12] and primary amines (Table 2). Generally, the reation was compatible with various α-substituted 2-(*o*-iodophenoxy)acyl chlorides, and gave the corresponding *N*-substituted 2*H*-1,4-benzoxazin-3-(4*H*)-ones in good to excellent yields. Both aliphatic and aromatic amines could smoothly undergo the reaction and gave satisfying yields. Higher temperatures and longer reaction times were usually required when aromatic amines were employed (entries 5-9, 13-16 and 18). The aromatic amines with electron-donating groups were more reactive and gave better results (entries 6, 8 and 14). While the reactions of those aromatic amines bearing electron-withdrawing groups afforded relatively lower yields, and longer reaction times were required (entries 9, 10 and 16). *p*-Nitroaniline even failed to react, because of its particularly weak nucleophilicity (entry 10). Racemic α-phenylethylamine gave relatively lower yield, which might result from the steric hindrance (entry 4 *vs* entry 3).

Table 2. CuI-catalyzed one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones from 2-(*o*-iodophenoxy)acyl chlorides and primary amines[a]



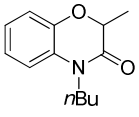
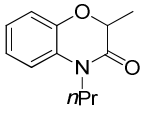
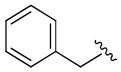
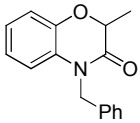
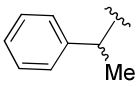
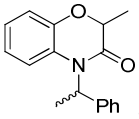
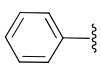
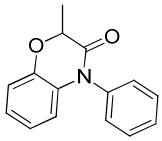
Entry	R^1	R^2	Product	Yield (%)[b]
1	Me	*n*Bu	 **3a**	95
2	Me	*n*Pr	 **3b**	94
3	Me		 **3c**	82
4	Me		 **3d**	73
5	Me		 **3e**	88[c]

Table 2. Continued

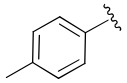
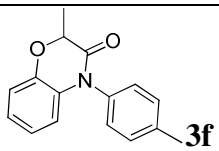
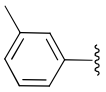
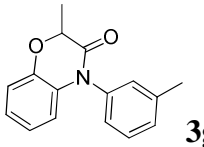
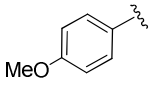
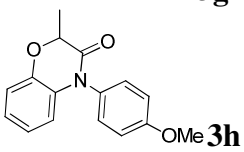
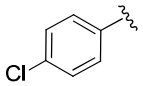
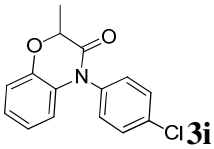
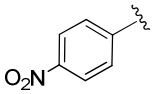
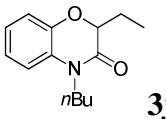
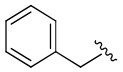
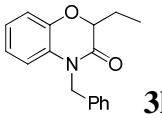
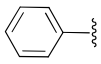
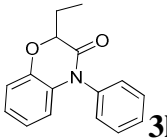
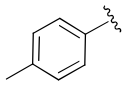
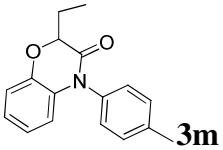
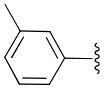
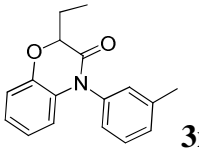
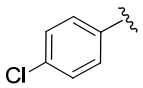
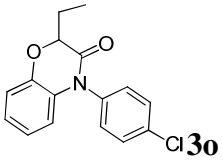
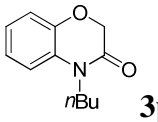
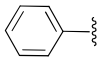
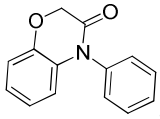
Entry	R^1	R^2	Product	Yield (%)[b]
6	Me		 **3f**	91[c]
7	Me		 **3g**	87[c]
8	Me		 **3h**	95[c]
9	Me		 **3i**	71[d]
10	Me		-	trace[d]
11	Et	*n*Bu	 **3j**	91
12	Et		 **3k**	80
13	Et		 **3l**	86[c]
14	Et		 **3m**	90[c]
15	Et		 **3n**	86[c]
16	Et		 **3o**	68[d]

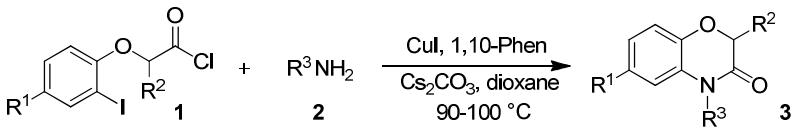
Table 2. Continued

Entry	R^1	R^2	Product	Yield (%)[b]
17	H	*n*Bu	 **3p**	95
18	H		 **3q**	87[c]

[a]Reaction conditions: **1** (0.50 mmol), **2** (0.55 mmol), CuI (0.025 mmol, 5 mol%), ligand (0.05 mmol, 10 mol%), and base (1.2 mmol, 2.4 equiv) in solvent (2 mL) under N_2 at 85 °C for 24 h. [b]Isolated yield. [c]At 100 °C for 28 h. [d]At 100 °C for 36 h.

We then tried to investigate the generality of the methodology by varying the substituents on the aryls of 2-(*o*-iodophenoxy)acyl chlorides (Table 3). Generally, the acyl chlorides **1** with various substituents on the aryl reacted smoothly and afforded good to excellent yields of **3**, though slightly higher temperature was required. Substrates **1** bearing electron-donating groups proceeded faster and gave better results (entries 1-4). The acyl chlorides with electron-withdrawing groups were less reactive (entries 5-7). However, once higher temperature and longer reaction time were provided, the yields could be obviously improved (entries 5 and 7). The reaction between 2-(4-bromo-2-iodophenoxy)acetyl chloride and aniline afforded an inseparable mixture, which might result from intermolecular reactions (entry 6).

Table 3. CuI-catalyzed one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones using 2-(*o*-iodophenoxy)acyl chlorides with different substituents[a]



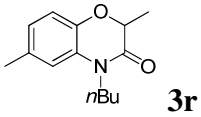
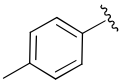
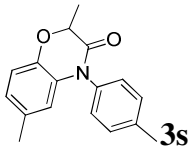
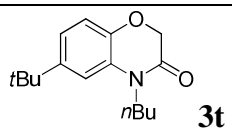
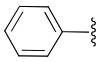
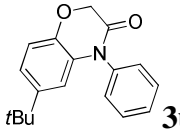
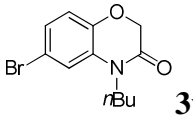
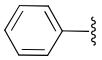
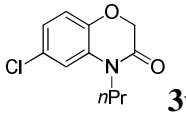
Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	Me	Me	*n*Bu	 **3r**	92
2	Me	Me		 **3s**	85[c]

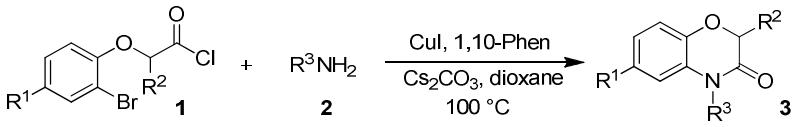
Table 3. Continued

Entry	R^1	R^2	R^3	Product	Yield (%)[b]
3	*t*Bu	H	*n*Bu	 **3t**	87
4	*t*Bu	H		 **3u**	82[c]
5	Br	H	*n*Bu	 **3v**	70 81[c]
6	Br	H		-	-[d]
7	Cl	H	*n*Pr	 **3w**	73 84[c]

[a]Reaction conditions: **1** (0.50 mmol), **2** (0.55 mmol), CuI (0.025 mmol, 5 mol%), ligand (0.05 mmol, 10 mol%), and base (1.2 mmol, 2.4 equiv) in solvent (2 mL) under N_2 at 90 °C for 24 h. [b]Isolated yield. [c]At 100 °C for 28 h. [d]An inseparable mixture was obtained.

Bromides are more economical and accessible than iodides. Therefore, we then focused on extending this protocol by using 2-(*o*-bromophenoxy)acyl chlorides and primary amines (Table 4). It was found that higher temperature (100 °C) and longer reaction times (30-36 h) were required in these cases. Although the results were slightly inferior to those obtained with 2-(*o*-iodophenoxy)acyl chlorides, the desired products could be generally obtained in good yields, showing that our protocol was also applicable for the reactions using bromides (entries 1-10).

Table 4. CuI-catalyzed one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones using 2-(*o*-bromophenoxy)acyl chlorides[a]



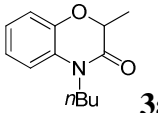
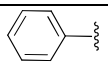
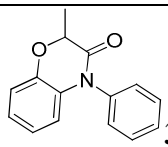
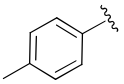
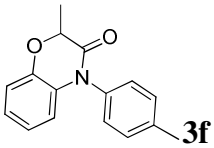
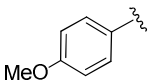
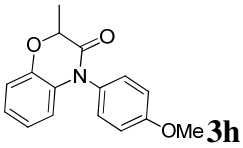
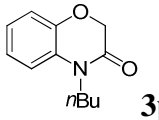
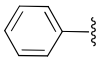
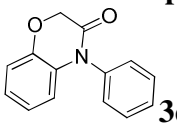
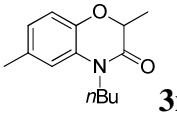
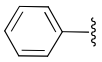
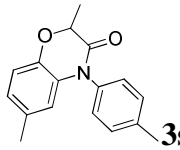
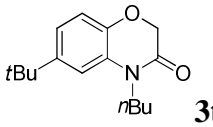
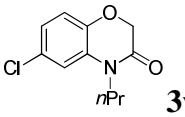
Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	H	Me	*n*Bu	 **3a**	90

Table 4. Continued

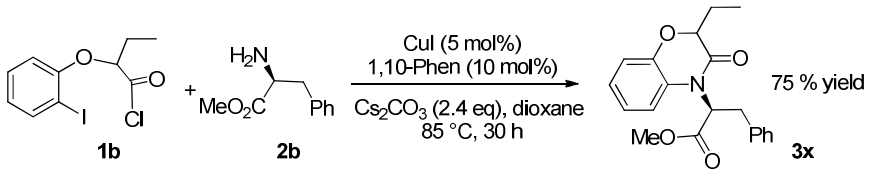
Entry	R^1	R^2	R^3	Product	Yield (%)[b]
2	H	Me		 **3e**	81[c]
3	H	Me		 **3f**	83[c]
4	H	Me		 **3h**	87
5	H	H	*n*Bu	 **3p**	88
6	H	H		 **3q**	80[c]
7	Me	Me	*n*Bu	 **3r**	84
8	Me	Me		 **3s**	78[c]
9	*t*Bu	H	*n*Bu	 **3t**	82
10	Cl	H	*n*Pr	 **3w**	65[c]

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (0.55 mmol), CuI (0.025 mmol, 5 mol%), ligand (0.05 mmol, 10 mol%), and base (1.2 mmol, 2.4 equiv) in solvent (2 mL) under N_2 at 100 °C for 28 h. [b]Isolated yield. [c]At 100 °C for 36 h.

Larger scale experiments for the synthesis of **3a** and **3e** from **1a** and the corresponding amines were also investigated (5 mmol scale), and the results remained almost the same (92% and 84% yield, respectively), though longer reaction times were required (at 85 °C for 28 h and at 100 °C for 36 h, respectively).[13]

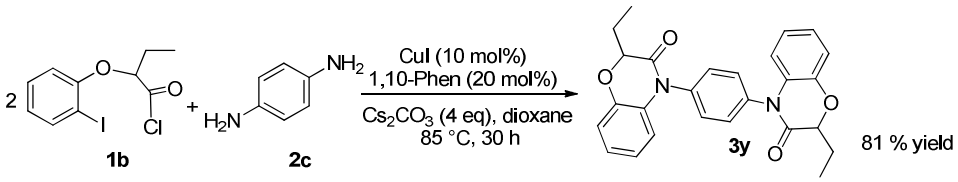
Finally, the copper-catalyzed one-pot strategy could be successfully applied to the synthesis of more complex compounds.

It was observed that a chiral primary amine **2b** with an ester group, which might be sensitive to base, could also be tolerated in the cascade process and reacted with **1b** smoothly to give the corresponding product **3x** (Scheme 2).[14]



Scheme 2. One-pot synthesis of (2*S*)-methyl 2-(2-ethyl-3-oxo-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)-3-phenylpropanoate.

Bifunctional *p*-phenylenediamine **2c** could also successfully react with 2 equiv. of **1b** to afford the corresponding symmetric derivative 4,4'-(1,4-phenylene)bis(2-ethyl-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-one **3y** (Scheme 3).



Scheme 3. One-pot synthesis of 4,4'-(1,4-phenylene)bis(2-ethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one.

Conclusions

In conclusion, we have developed a facile and efficient one-pot protocol for the synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones *via* a CuI-catalyzed cascade condensation/C-N coupling process. The starting 2-(*o*-haloaryloxy)acyl chlorides could be conveniently prepared and utilized directly without purification. It enables the assembly of various 2*H*-1,4-benzoxazin-3-(4*H*)-ones in good to excellent yields from a variety of 2-(*o*-haloaryloxy)acyl chlorides and primary amines.. Comparing with the previous reported one-pot methods,[9] this method could directly and conveniently introduce various substituents on the 4-position of the products (by simply varying the starting amines). As little as 5 mol% of the Cu(I)-catalyst worked well. And more complex compounds could also be smoothly assembled *via* this strategy. The readily available materials, convenient procedures, and broad application scopes would make the present protocol useful and

practical. Therefore, this method may be attractive for the synthesis of the related biologically and pharmaceutically interesting molecules.

Experimental Section

General. All reagents and solvents were pure analytical grade materials purchased from commercial sources and were used without further purification, if not stated otherwise. All melting points are uncorrected. The IR spectra were recorded on a FT-IR spectrophotometer. The NMR spectra were recorded in $CDCl_3$ on a 400 M Hz instrument with TMS as internal standard. Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets); td (triplet of doublets); br s (broad singlet), etc. and coupling constants are given in hertz. Thin-Lay Chromatography (TLC) was carried out with 0.2 mm thick silica gel plates (GF254). Visualization was accomplished by UV light. The columns were hand packed with silica gel 60 (300-400). All reactions were carried out in an over-dried Schlenk tube equipped with a magnetic stir bar under N_2 atmosphere. Unknown compound was additionally confirmed by HRMS and Elemental Analysis. Mass spectra were obtained using ESI ionization.

2-*o*-Haloaryloxy acids

Method A (R^1 = H, Me, tBu). 4-Substituted-*o*-iodophenol (0.02 mol) was added to a solution of NaOH (0.04 mol, 2 equiv.) in water (10 mL), then 2-bromocarboxylic acid (0.03 mol, 1.5 equiv.) was added slowly at 40 °C. The mixture was heated to 100 °C and stirred for 6 h. The mixture was cooled to room temperature and acidified to pH 1-2 with concentrated HCl. The oil fraction was extracted with ethyl ether (3 × 20 mL). The ether fraction was further extracted with 10% $NaHCO_3$ (3 × 20 mL). The $NaHCO_3$ solution was washed with ethyl ether (3 × 10 mL), and then acidified to pH 1-2 with concentrated HCl. The precipitate was filtered off, washed with water and dried in air to obtain the corresponding 2-*o*-haloaryloxy acid (in 81~93% yield; used without further purification).

Method B (R^1 = Cl, Br). A mixture of 4-substituted-*o*-iodophenol (0.02 mol), 2-bromocarboxylic acid (0.024 mol, 1.2 equiv.), anhydrous potassium carbonate (0.024 mol, 1.2 equiv.) and dry DMF (30 mL) was heated at 90 °C with stirring for 6 h. The mixture was cooled to room temperature. Ethyl acetate (50 mL) and water (50 mL) was added, and the mixture was acidified to pH 1-2 with concentrated HCl. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine (3 × 20 mL) and extracted with 10% $NaHCO_3$ (3 × 20 mL). The $NaHCO_3$ solution was washed with ethyl ether (3 × 10 mL), and then acidified to pH 1-2 with concentrated HCl. The precipitate was filtered off, washed with water and dried in air to obtain the corresponding 2-*o*-haloaryloxy acid (in 63 ~72% yield; used without further purification).

2-(*o*-Haloaryloxy)acyl chlorides (1). Thionyl chloride (40 mmol, 2 equiv.) was added slowly to a solution of 2-*o*-haloaryloxy acid (20 mmol) in $CHCl_3$ (10 mL) at 0 °C. The mixture was allowed to be heated to 70 °C and stirred for 3-4 h. After evaporating $CHCl_3$ and excess thionyl chloride under reduced pressure, the corresponding 2-(*o*-haloaryloxy)acyl chloride **1** could be obtained (it can be stored in refrigerator and used directly without further purification).

2*H*-1,4-Benzoxazin-3-(4*H*)-ones (3). An oven-dried Schlenk tube was charged with a magnetic stir bar, CuI (0.025 mmol, 5 mol%), 1,10-Phen (0.05 mmol, 10 mol%), and Cs_2CO_3 (1.2 mmol, 2.4 equiv). The Schlenk tube was capped, and then evacuated and backfilled with nitrogen (3 times). Under a positive pressure of nitrogen, a solution of amine **2** (0.55 mmol) in dioxane (1 mL) was added *via* syringe. Then a solution of 2-(*o*-haloaryloxy)acyl chloride **1** (0.5 mmol) in dioxane (1 mL) was added dropwise *via* syringe (for about 15 min) and the mixture was prestirred at room temperature for 15 min. The Schlenk tube was sealed and allowed to stir at the indicated temperature for 24-36 h. The reaction mixture was directly passed through Celite and rinsed with an additional 30 mL of AcOEt. The combined filtrate was concentrated and purified by column chromatography on silica gel using ethyl acetate/petrol ether (1:10 ~ 1:6, v:v) as eluate to give the corresponding product **3**.

All the products were characterized with ^{1}H NMR and ^{13}C NMR; new compounds were additionally characterized by HRMS and Elemental Analysis. Spectral data of the representative products are given below.

Selected spectral data of the products (3)

4-Butyl-2-methyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (3a). Oil; IR (neat): *v* 3353, 3050, 2959, 2865, 1681, 1500, 1466, 1402, 1301, 1273, 1110, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96-7.05 (m, 4H), 4.61 (q, *J* 6.8 Hz, 1H), 3.92 (d, *J* 7.6 Hz, 2H), 1.59-1.68 (m, 2H), 1.55 (d, *J* 6.8 Hz, 3H), 1.36-1.45 (m, 2H), 0.96 (t, *J* 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 144.6, 128.8, 123.6, 122.6, 117.4, 114.7, 73.4, 41.2, 29.2, 20.1, 16.4, 13.8; HRMS (ESI): *m/z* calcd. for $C_{13}H_{17}NO_2$ $[M + H]^+$: 220.1332, found: 220.1339; Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.01; H, 7.87; N, 6.22.

2-Methyl-4-phenyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (3e).[10b] White solid; mp 79-81 °C (lit.[10b] 78-80 °C). IR (KBr): *v* 3348, 3060, 2932, 2860, 1688, 1499, 1462, 1372, 1271, 1104, 1049, 753, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.56 (m, 2H), 7.46 (t, *J* 7.6 Hz, 1H), 7.28 (d, *J* 8.0 Hz, 2H), 7.05-7.07 (m, 1H), 6.98-7.02 (m, 1H), 6.84-6.88 (m, 1H), 6.42-6.44 (m, 1H), 4.81 (q, *J* 6.8 Hz, 1H), 1.67 (d, *J* 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 144.2, 136.4, 130.9, 129.9, 128.8, 128.7, 124.0, 122.4, 117.3, 116.7, 74.0, 16.3.

4-(4-Methoxyphenyl)-2-methyl-2*H*-benzo[*b*]-[1,4]oxazin-3(4*H*)-one (3h).[10a] White solid; mp 151-153 °C; IR (KBr): *v* 3361, 3067, 2959, 2835, 1690, 1611, 1497, 1462, 1371, 1297, 1253, 1105, 1030, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, *J* 8.8 Hz, 2H), 7.02-7.05 (m, 3H), 6.96-7.00 (m, 1H), 6.84-6.88 (m, 1H), 6.45 (dd, J_1 1.2 Hz, J_2 8.0 Hz, 1H), 4.80 (q, *J* 6.8 Hz, 1H), 3.87 (s, 3H), 1.65 (d, *J* 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 159.5, 144.1, 131.1, 129.8, 128.8, 123.9, 122.4, 117.2, 116.7, 115.2, 74.0, 55.5, 16.4.

4-Benzyl-2-ethyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (3k). White solid; mp 59-61 °C; IR (KBr): *v* 3332, 3035, 2973, 2865, 1669, 1591, 1500, 1464, 1322, 1278, 1241, 1134, 1057, 753, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.35 (m, 2H), 7.24-7.28 (m, 3H), 6.95-7.03 (m, 2H), 6.85-6.89 (m, 2H), 5.25 (d, *J* 16.0 Hz, 1H), 5.07 (d, *J* 16.0 Hz, 1H), 4.62 (q, *J* 4.4 Hz, 1H), 1.92-2.06 (m, 2H), 1.14 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 144.1, 136.2, 128.87, 128.85, 127.4, 126.5, 124.0, 122.5, 117.4, 115.4, 78.4, 45.1, 23.8, 9.6; HRMS (ESI): *m/z* calcd. for $C_{17}H_{17}NO_2$ $[M + H]^+$: 268.1332, found: 268.1342; Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24; found: C, 76.17; H, 6.42; N, 5.46.

4-Butyl-2,6-dimethyl-2H-benzo[*b*][1,4]oxazin -3(4*H*)-one (3r). Oil; IR (neat): *v* 3349, 3038, 2959, 2872, 1682, 1511, 1446, 1270, 1241, 1111, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, *J* 8.0 Hz, 1H), 6.76-6.79 (m, 2H), 4.56 (q, *J* 6.8 Hz, 1H), 3.89 (t, *J* 7.6 Hz, 2H), 2.34 (s, 3H), 1.60-1.67 (m, 2H), 1.53 (d, *J* 6.8 Hz, 3H), 1.36-1.45 (m, 2H), 0.97 (t, *J* 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 142.4, 132.1, 128.6, 124.0, 117.1, 115.2, 73.4, 41.2, 21.2, 20.1, 16.3, 13.81, 13.79; HRMS (ESI): *m/z* calcd. for $C_{14}H_{19}NO_2$ $[M + H]^+$: 234.1489, found: 234.1498; Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00; found: C, 72.32; H, 8.33; N, 6.09.

6-(*tert*-Butyl)-4-butyl-2*H*-benzo[*b*][1,4]oxa-zin-3(4*H*)-one (3t).[10b] Oil; IR (neat): *v* 3363, 3045, 2960, 2872, 1689, 1519, 1436, 1385, 1280, 1265, 1047, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.00-7.03 (m, 2H), 6.91 (d, *J* 8.0 Hz, 1H), 4.57 (s, 2H), 3.96 (t, *J* 7.6 Hz, 2H), 1.63-1.71 (m, 2H), 1.41-1.49 (m, 2H), 1.32 (s, 9H), 0.99 (t, *J* 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 145.8, 143.1, 127.8, 120.5, 116.4, 112.1, 67.7, 40.6, 34.5, 31.5, 29.1, 20.1, 13.8.

6-Bromo-4-butyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (3v). Oil; IR (neat): *v* 3365, 3076, 2958, 2870, 1693, 1495, 1431, 1379, 1268, 1230, 1048, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.09-7.11 (m, 2H), 6.85-6.87 (m, 1H), 4.58 (s, 2H), 3.89 (t, *J* 7.6 Hz, 2H), 1.61-1.68 (m, 2H), 1.37-1.46 (m, 2H), 0.98 (t, *J* 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 144.5, 130.0, 126.3, 118.5, 117.8, 114.9, 67.5, 41.0, 29.0, 20.0, 13.7; HRMS (ESI): *m/z* calcd. for $C_{12}H_{14}BrNO_2$ $[M + H]^+$: 284.0281, found: 284.0288; Anal. Calcd. for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93; found: C, 50.41; H, 4.87; N, 4.79.

4,4'-(1,4-Phenylene)bis(2-ethyl-2*H*-benzo[*b*][1,4]-oxazin-3(4*H*)-one) (3y). White solid; mp 195-197 °C; IR (KBr): *v* 3371, 3060, 2963, 2875, 1695, 1499, 1465, 1373, 1303, 1277, 1053, 978, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 4H), 7.01-7.09 (m, 4H), 6.89 (t, *J* 7.6 Hz, 2H), 6.55 (d, *J* 8.4 Hz, 2H), 4.65 (q, *J* 4.4 Hz, 2H), 1.96-2.11 (m, 4H), 1.16 (t, *J* 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 144.0, 136.4, 130.4, 130.3, 124.4, 122.5, 117.5, 116.9, 78.8, 23.7, 9.5; HRMS (ESI): *m/z* calcd. for $C_{26}H_{24}N_2O_4$ $[M + H]^+$: 429.1809, found: 429.1821; Anal. Calcd. for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54; found: C, 72.62; H, 5.70; N, 6.38.

Supplementary Material Available

Experimental procedures, characterization data (for all the products), copies of ^1H and ^{13}C NMR spectra associated with this paper can be found in the online version.

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14. The product was a mixture of two diastereoisomers. The mole ratio was about 1.2:1 (approximately determined by ^{1}H NMR).

