An efficient cascade synthesis of various 2*H*-1,4-benzoxazin-3-(4*H*)-ones from *o*-halophenols and 2-halo-amides catalyzed by CuI†

Dingben Chen,[a,b] Guodong Shen[a] and Weiliang Bao*[a]

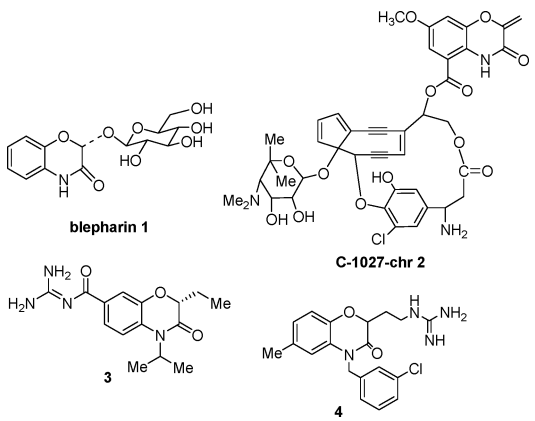
Received 30th March 2009, Accepted 2nd July 2009
First published as an Advance Article on the web 4th August 2009
DOI: 10.1039/b906210f

A novel and efficient one-pot cascade synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones has been developed through copper-catalyzed coupling of *o*-halophenols and 2-halo-amides. Various 2*H*-1,4-benzoxazin-3-(4*H*)-ones with diversity at three substituents on their scaffold have been synthesized conveniently in good to excellent yields.

Introduction

2*H*-1,4-Benzoxazin-3-(4*H*)-one[1] is an important heterocycle scaffold that is a component of natural and designed synthetic bioactive compounds, ranging from herbicides and fungicides to therapeutical usable drugs. For example, blepharin **1** and other glycosides with the 2-hydroxy-2*H*-1,4-benzoxazine-3(4*H*)-one skeleton isolated from gramineous plants, such as maize, wheat, rye and rice, have been suggested to act as plant resistance factors against microbial diseases and insects.[2a] C-1027-chr **2** is an active ingredient of enediyne antitumor antibiotics.[2b,c] In *N*-substituted products of 2*H*-1,4-benzoxazine-3(4*H*)-one, **3** is a potential drug for treating heart disease[2d] and **4** is an inhibitor of bacterial histidine protein kinase.[2e] In addition, other biological activities have been reported, including serotonin-3(5-HT_3) receptor antagonists, potassium channel modulators, antirheumatic agents, and antihypertensive agents.[2f]

Two common approaches to 2*H*-1,4-benzoxazin-3-(4*H*)-ones employ 2-nitrophenols or 2-aminophenols as the precursors. The first approach includes three steps of *O*-alkylation, nitro reduction and intramolecular *N*-substitution.[3a,b] In the latter approach, 2-aminophenols are usually treated with 2-haloalkanoyl chlorides or bromides to form 2-amidophenols, which then undergo intramolecular *O*-alkylation on heating in the presence of a base.[3c,d] The above two approaches might suffer from inconvenient operations and a limited number of suitable substrates for diverse synthesis. Recently, Dai group developed microwave-assisted one-pot synthetic methods to construct 2*H*-1,4-benzoxazin-3-(4*H*)-ones,[2f,4] which started from 2-aminophenols or *N*-alkyl-2-aminophenols. However, the substituent diversity in the products is limited, and for example, it is difficult to synthesize *N*-aryl-2*H*-1,4-benzoxazin-3-(4*H*)-ones. Therefore, concise and efficient methods to give these heterocyclic motifs are still in demand.



In the past decade, considerable progress has been made in the area of copper-catalyzed Ullman *N*-arylations.[5] Intramolecular Ullmann coupling reactions have been explored to construct *N*-heterocycles. In particular, one-pot strategies for the synthesis of various useful heterocyclic compounds through copper-catalyzed coupling have received much attention because of their more convenient manipulations and good efficiencies. For example, our group[6a,b] and others[6c–f] have developed highly efficient copper catalyst systems to build *N*-heterocycles, including 2-iminobenzo-1,3-oxathioles, 2,3-dihydro-1,4-benzodioxins, benzimidazoles, quinazolinones, indoles and pyrrolo[1,2*a*]-quinoxalines. To the best of our knowledge, there is no example of constructing 2*H*-1,4-benzoxazin-3-(4*H*)-ones *via* a one-pot copper-catalyzed coupling process. Herein, we report a novel and efficient copper-catalyzed cascade one-pot reaction of *o*-halophenols with 2-halo amides to synthesize the title *N*-heterocycle compounds with diversity at three substituents on their scaffold

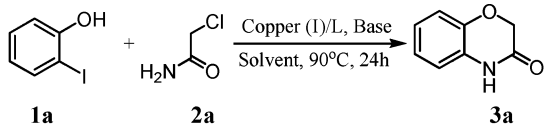
Results and discussion

In our preliminary experiments, *o*-iodophenol **1a** and 2-chloroacetamide **2a** were chosen as model substrates for the optimization of the reaction conditions including the catalysts, ligands, bases, and solvents under nitrogen atmosphere. The reaction was subjected to the following typical Ullmann coupling conditions: CuI (10 mol%), 1,10-phenanthroline ($\mathbf{L_1}$, 20 mol%), Cs_2CO_3 (2 equiv.) in dioxane at 90 °C. To our delight, the starting materials disappeared and the anticipated product **3a** was obtained in 82% yield after 24 h (Table 1, entry 1). We then investigated the

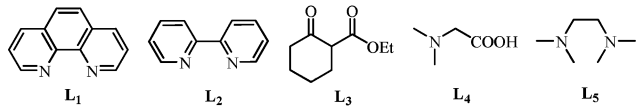
[a]*Department of Chemistry, Zhejiang University, Xi Xi Campus, Hangzhou, 310028, Zhejiang, P. R. China. E-mail: wlbao@css.zju.edu.cn; Fax: +86 (571) 88273814; Tel: +86 (571) 88273814*
[b]*College of Pharmaceutical and Chemical Engineering, Taizhou University, Linhai, 317000, Zhejiang, P. R. China*

† Electronic supplementary information (ESI) available: Experimental details and NMR spectra. See DOI: 10.1039/b906210f

Table 1 Optimization of the reaction conditions for synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-one[a]



1a **2a** **3a**



L_1 L_2 L_3 L_4 L_5

Ligand (L_1-L_5)

Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	L_1	Cs_2CO_3	Dioxane	82
2	CuI	L_1	Cs_2CO_3	DME	54
3	CuI	L_1	Cs_2CO_3	PhMe	23
4	CuI	L_1	Cs_2CO_3	DMF	64
5	CuI	L_1	Cs_2CO_3	DMSO	72
6	CuI	L_1	Cs_2CO_3	NMP	75
7	CuI	L_1	K_3PO_4	Dioxane	17
8	CuI	L_1	K_2CO_3	Dioxane	20
9	CuBr	L_1	Cs_2CO_3	Dioxane	80
10	Cu_2O	L_1	Cs_2CO_3	Dioxane	55
11	CuI	L_2	Cs_2CO_3	Dioxane	42
12	CuI	L_3	Cs_2CO_3	Dioxane	17
13	CuI	L_4	Cs_2CO_3	Dioxane	Trace
14	CuI	L_5	Cs_2CO_3	Dioxane	47
15	CuI	—	Cs_2CO_3	Dioxane	36
16	CuI	L_1	Cs_2CO_3	Dioxane	83[c]
17	CuI	L_1	Cs_2CO_3	Dioxane	95[d]

[a] *Reagents and conditions*: *o*-iodophenol **1a** (0.5 mmol), 2-chloroacetamide **2a** (0.5 mmol), copper source (0.05 mmol), ligand (0.1 mmol) and base (1.0 mmol) in solvent (2.0 mL) under N_2 at 90 °C for 24 h. [b] Isolated yield. [c] **2a** (0.6 mmol). [d] **1a** (0.6 mmol), base (1.1 mmol).

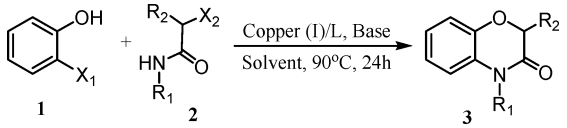
effect of the solvents. However, the reaction was less successful in other solvents such as DME, PhMe, DMF, DMSO or NMP (Table 1, entries 2–6). The yield was lowest in toluene (only 23%), but the yield in DMSO or NMP was acceptable. The bases Cs_2CO_3, K_2CO_3 and K_3PO_4 were screened, Cs_2CO_3 proving to be the most effective (Table 1, entries 1, 7 and 8). The copper salts CuI, CuBr, Cu_2O were also tested in dioxane (Table 1, entries 1, 9 and 10), with CuI showing the best activity. We attempted to use different ligands (L_1–L_5), but 2,2′-bipyridine and TEMED were not suitable for this reaction, with only 42% and 47% isolated yield being obtained (Table 1, entries 11 and 14). Ethyl 2-oxocyclohexanecarboxylate (Table 1, entry 12) was not beneficial for this process either, though it was an efficient and versatile ligand in our group's previous work.[7] Only trace amounts of product was observed when *N*,*N*-dimethylglycine was tried (Table 1, entry 13). In the absence of ligand, the product was gained in 36% yield (Table 1, entry 15); maybe the reactant 2-chloroacetamide or the intermediate 2-(2-iodophenoxy) acetamide acted as the ligand to promote the reaction.[8] Finally, we changed the ratio of *o*-iodophenol to 2-chloroacetamide. When the ratio was 1:1.2, the product yield was enhanced only a little (Table 1, entry 16). However, the isolated yield increased greatly (95%, Table 1, entry 17) when the ratio was 1.2:1 and 2.2 equivalents of Cs_2CO_3 were used. Therefore, the optimized conditions were as follows: a combination of *o*-iodophenol **1a** (1.2 equiv.), 2-chloroacetamide **2a** (1.0 equiv.), CuI (10 mol%) and 1,10-phenanthroline (20 mol%) in the presence of Cs_2CO_3 (2.2 equiv.) as base in dioxane.

Using the above optimized conditions, we investigated the substrate scope. Firstly, the reactions of 2-iodophenol **1a** with various *N*-substituted-2-haloacetamides **2** were studied. As shown in Table 2, most of the substrates examined provided good to excellent yields. 2-Chloro-*N*-alkylacetamides reacted with *o*-iodophenol to give the corresponding products in good yield (Table 2, entries 1 and 3), although the yield with 2-chloro-*N*-phenylacetamide was higher. 2-Halo-*N*-phenylacetamides and substrates with electron-donating groups on the phenyl ring showed high reactivity, and excellent yields resulted (Table 2, entries 4, 5, 7 and 10). In contrast, substrates with electron-withdrawing groups at the *N*-position showed low reactivities (Table 2, entries 8 and 9); only 55% and 45% yields were obtained for 4-(3-chlorophenyl)-(2*H*)-1,4-benzoxazin-3(4*H*)-one and 4-(pyridin-2-yl)-(2*H*)-1,4-benzoxazin-3(4*H*)-one respectively, even after the reaction time was prolonged to 36 h. When there were both R_1 and R_2 substituents on the 2-halo-acetamide, the reactions went well; in particular, the yield of 2-methyl-4-phenyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one was excellent (Table 2, entry 10). Comparing the yield of **3j** with **3b**, it was obvious that the R_2 group showed a little steric effect. In addition, 2-bromophenol could also react with 2-halo-acetamides to give the corresponding products in moderate to good yield at reflux (Table 2, entries 2 and 6).

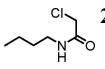
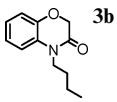
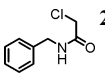
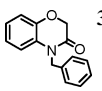
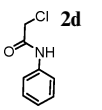
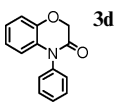
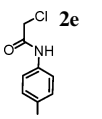
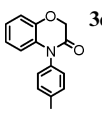
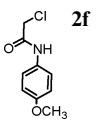
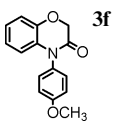
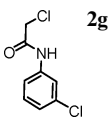
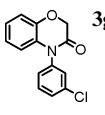
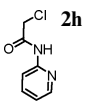
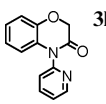
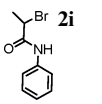
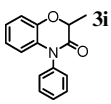
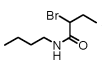
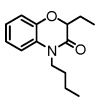
We further investigated the scope and the generality of the method by varying the *o*-iodophenols, which could be easily derived from the *para*-substituted phenols[9a] (Table 3, entries 1–10). Generally the substituted *o*-iodophenols could treated with 2-halo-amides and moderate to excellent yields were obtained, though higher temperatures were required. The relative reactivity of substituted *o*-iodophenols was in the following order: 4-*tert*-butyl > 4-methyl > 4-chloro. The 2-iodophenol bearing electron-donating groups reacted with 2-chloro-*N*-phenylacetamide to afford products in excellent yield (Table 3, entries 4 and 5), while those bearing electron-withdrawing groups reacted slowly and lower yields were obtained (Table 3, entries 6 and 10). The product yield of 4-butyl-6-methyl-2*H*-1,4-benzoxazin-3-(4*H*)-one **3r** derived from **1d** and **2b** (Table 3, entry 8) was lower than for 4-butyl-2*H*-1,4-benzoxazin-3-(4*H*)-one (Table 2, **3b**), only 51% yield. This indicated that the reactivity of *N*-alkyl amides was a little bit low. When the temperature mixture was refluxed, the yield was enhanced greatly, as shown in Table 3, entry 7, the yield of 4-butyl-6-*t*-butyl-2*H*-1,4-benzoxazin-3-(4*H*)-one being 98%. In addition, 2-methyl- or ethyl-substituted substrates of 2-bromoacetamide also reacted with substituted 2-iodophenols to give the corresponding products at reflux (Table 3, entries 9 and 10).

A pathway for the formation of 2*H*-1,4-benzoxazin-3-(4*H*)-ones is proposed in Scheme 1. The target products are afforded *via* two steps. Firstly, in the presence of Cs_2CO_3, the intermolecular nucleophilic substitution occurred between *o*-iodophenol and 2-halo-amide, and intermediate **I** would be formed (step **a**). We had isolated the intermediate **I** in the reaction of **1a** with **2e** under the standard conditions (see ESI†, compound **5**). The reaction of *o*-iodophenol with 2-chloro-*N*-*tert*-butylacetamide cannot result in the desired product because of steric hindrance, but the intermediate **I** was isolated in >99% yield (see ESI†, compound **4**). Thus we conclude that this cyclization reaction occurs *via* the proposed two-step pathway.

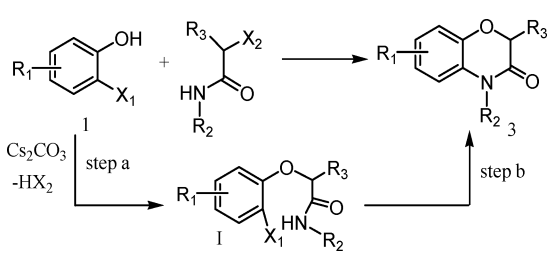
Table 2 CuI-catalyzed one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones from 2-halophenol and 2-halo-acetamides[a]



1 2 3

Entry	2-Halophenol	2-Halo-amide	Product	Yield (%)[b]
1	 **1a** (x = I)	 **2b**	 **3b**	84
2	**1b** (x = Br)			55[c]
3	**1a**	 **2c**	 **3c**	71
4	**1a**	 **2d**	 **3d**	97
5	**1a** (x = I)	 **2e**	 **3e**	98
6	**1b** (x = Br)			80[c]
7	**1a**	 **2f**	 **3f**	86
8	**1a**	 **2g**	 **3g**	55[d]
9	**1a**	 **2h**	 **3h**	45[d]
10	**1a**	 **2i**	 **3i**	97
11	**1a**	 **2j**	 **3j**	73[c]

[a] *Reagents and conditions*: 2-Halo-phenol (0.6 mmol), 2-halo-amides (0.5 mmol), CuI (0.05 mmol), $\mathbf{L_1}$ (0.1 mmol) and Cs_2CO_3 (1.1 mmol, 2.2 equiv.) in dioxane (2.0 mL) under N_2. [b] Isolated yield. [c] At reflux. [d] 6 h.

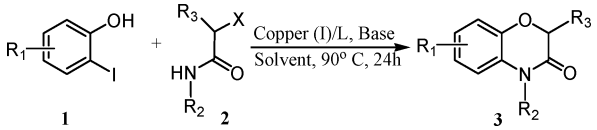


Scheme 1 Proposed reaction pathway for the one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones.

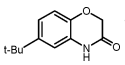
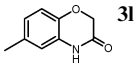
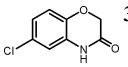
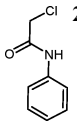
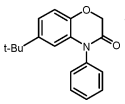
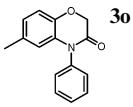
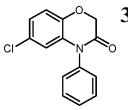
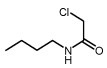
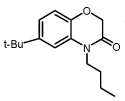
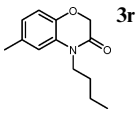
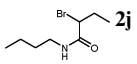
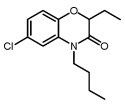
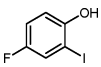
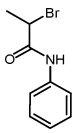
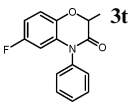
Conclusions

In conclusion, we have designed and developed a novel, efficient one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones under copper(I) catalysis, employing readily available starting materials. Various 2*H*-1,4-benzoxazin-3-(4*H*)-ones with diversity at three substituents on their scaffold were synthesized conveniently in good to excellent yields, and these should prove useful in pharmaceutical and biochemical fields. Further elaboration of this novel one-pot strategy for the synthesis of other heterocyclic compounds is ongoing in our laboratory.[11]

Table 3 CuI-catalyzed one-pot synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones from substituted *ortho*-iodophenol and 2-halo-acetamides[a]



1 2 3

Entry	2-Iodophenol	2-Halo-amides	Product	Yield (%)[b]
1	 **1c**	 **2a**	 **3k**	80
2	 **1d**	**2a**	 **3l**	71
3	 **1e**	**2a**	 **3m**	55
4	**1c**	 **2d**	 **3n**	99
5	**1d**	**2d**	 **3o**	98
6	**1e**	**2d**	 **3p**	83
7	**1c**	 **2b**	 **3q**	98[c]
8	**1d**	**2b**	 **3r**	51
9	**1e**	 **2j**	 **3s**	70[c]
10	 **1f**	 **2i**	 **3t**	64[c]

[a] *Reagents and conditions*: 2-iodophenol (0.6 mmol), 2-halo-amides **2a** (0.5 mmol), CuI (0.05 mmol), $\mathbf{L_1}$ (0.1 mmol) and Cs_2CO_3 (1.1 mmol, 2.2 equiv.) in dioxane (2.0 mL) under N_2. [b] Isolated yield. [c] At reflux.

Experimental

All reagents and solvents were pure analytical-grade materials purchased from commercial sources and were used without further purification, if not stated otherwise. 4-Substituted-*o*-iodophenols and *N*-substituted 2-halo-amides were prepared according to the literature.[9a–c] All melting points are uncorrected. The NMR spectra were recorded in $CDCl_3$ on a 400 MHz instrument with TMS as internal standard. 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 (200–300). All reactions were carried out in an oven-dried Schlenk tube equipped with a magnetic stir bar under N_2 atmosphere. New compounds were additionally confirmed by ^{13}C NMR and elemental analysis. Mass spectra were obtained using EI ionization, and IR spectra were taken in an ATR apparatus.

General procedure for the synthesis of 2*H*-1,4-benzoxazin-3-(4*H*)-ones (3)

An oven-dried Schlenk tube equipped with a Teflon valve was charged with a magnetic stir bar, CuI (10 mg, 0.05 mmol, 10 mol%), Cs_2CO_3 (359 mg, 1.1 mmol), 2-halophenol **1** (0.60 mmol), 2-halo-amides **2** (0.50 mmol), and 1,10-phenanthroline (20 mg, 0.10 mmol, 20 mol%). The tube was evacuated and backfilled with N_2 (this procedure was repeated 3 times). Under a counter-flow of N_2, dioxane (2.0 mL) was added by syringe and the mixture was stirred for about 24 h at 90 °C. The reaction mixture was cooled

to room temperature, ethyl acetate (20 mL) was added, and the resulting suspension was filtered. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (PE–EtOAc = 10:1–2:1, v/v) to provide the desired product **3**.

(2*H*)-1,4-Benzoxazin-3(4*H*)-one (3a). A white solid;[10a] Mp 168–170 °C; IR (neat) ν_{max}/cm^{-1} 3452.7, 3057.5, 2917.5, 1693.9, 1605.2, 1498.6, 1400.5, 1217.2, 1045.4 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 8.57 (s, 1H), 6.98–6.94 (m, 3H), 6.84–6.81 (m, 1H), 4.63 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 166.6, 143.6, 126.0, 124.2, 122.7, 116.7, 116.2, 67.0 ppm.

4-Butyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3b). A colorless oil; IR (neat) ν_{max}/cm^{-1} 3079.5, 2958.2, 1683.6, 1608.0, 1514.7, 1437.1, 1382.1, 1262.8, 1047.9 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.05–6.98 (m, 4H), 4.58 (s, 2H), 3.92 (t, J = 7.6 Hz, 2H), 1.69–1.61 (m, 2H), 1.46–1.36 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 164.1, 145.3, 128.4, 123.6, 122.6, 117.0, 114.8, 67.5, 40.8, 29.0, 20.0, 13.7 ppm. MS (EI) m/z 205 (M^+). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N 6.82; Found: C, 70.43; H, 7.26; N 6.95.

4-Benzyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3c). A white solid;[10b] Mp 68–70 °C; IR (neat) ν_{max}/cm^{-1} 3066.1, 2923.6, 1682.4, 1600.3, 1498.2, 1396.2, 1229.1, 1046.2 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.34–7.30 (m, 2H), 7.26–7.24 (m, 3H), 7.01–6.87 (m, 4H), 5.16 (s, 2H), 4.73 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 164.7, 145.3, 135.9, 128.9, 128.7, 127.5, 126.6, 124.0, 122.8, 116.9, 115.7, 67.7, 44.9 ppm.

4-Phenyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3d). A white solid;[10c] Mp 96–98 °C; IR (neat) ν_{max}/cm^{-1} 3034.1, 2969.5, 1678.9, 1593.8, 1491.8, 1373.9, 1276.2, 1048.2 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.56–7.52 (m, 2H), 7.48–7.45 (m, 1H), 7.30–7.28 (m, 2H), 7.06–7.04 (m, 1H), 7.01–6.97 (m, 1H), 6.87–6.83 (m, 1H), 6.44–6.42 (m, 1H), 4.78 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 164.3, 144.9, 135.8, 130.6, 130.0, 128.9, 126.7, 124.1, 122.6, 117.0, 116.9, 68.2 ppm.

4-p-Tolyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3e). A white solid;[10d] Mp 128–130 °C; IR (neat) ν_{max}/cm^{-1} 3092.2, 2969.4, 1679.9, 1599.6, 1493.2, 1376.5, 1275.6, 1046.4 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.34 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.04 (dd, J = 8.2, 3.2 Hz, 1H), 7.00–6.96 (m, 1H), 6.87–6.83 (m, 1H), 6.45 (dd, J = 8.0, 2.4 Hz, 1H), 4.77 (s, 2H), 2.43 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 164.3, 144.8, 138.8, 138.8, 133.0, 130.6, 128.4, 123.9, 122.5, 117.0, 68.1, 21.2 ppm.

4-(4-Methoxylphenyl)-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3f). A white solid;[10d] Mp 118–120 °C; IR (neat) ν_{max}/cm^{-1} 3073.2, 2917.5, 1685.0, 1607.0, 1542.5, 1509.5, 1498.2, 1373.5, 1244.8, 1027.6 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.21–7.19 (m, 2H), 7.05–7.02 (m, 3H), 7.00–6.96 (m, 1H), 6.88–6.83 (m, 1H), 6.47 (dd, J = 8.0, 0.8 Hz 1H), 4.77 (s, 2H), 3.86 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 164.5, 159.6, 144.8, 130.7, 129.7, 128.0, 123.9, 122.5, 116.9, 116.8, 115.2, 68.1, 55.5 ppm.

4-(3-Chlorophenyl)-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3g). A viscous oil; IR (neat) ν_{max}/cm^{-1} 3086.5, 2922.1, 1686.9, 1589.9, 1492.6, 1366.7, 1276.7, 1047.8 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.49–7.43 (m, 2H), 7.32 (d, 1H), 7.21–7.19 (m, 1H), 7.06–6.99 (m, 2H), 6.90 (t, J = 7.6 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H), 4.76 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 164.2, 144.8, 136.8, 135.4, 130.9, 130.1, 129.2, 129.1, 127.1, 124.4, 122.7, 117.1, 116.8, 68.0 ppm. MS (EI) m/z 259 (M^+). Anal. Calcd for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39; Found: C, 65.08; H, 3.97; N, 5.19.

4-(Pyridin-2-yl)-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3h). A white solid; Mp 97–98 °C; IR (neat) ν_{max}/cm^{-1} 3060.4, 2923.1, 1687.7, 1591.7, 1497.2, 1367.0, 1261.0, 1047.1 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 8.70 (d, J = 4.4 Hz, 1H), 7.96–6.91 (m, 1H), 7.44–7.41 (m, 2H), 7.08–6.99 (m, 2H), 6.90–6.86 (m, 1H), 6.44 (dd, J = 8.0, 0.4 Hz, 1H), 4.77 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 164.4, 150.2, 149.5, 144.9, 138.9, 129.3, 124.4, 124.1, 123.9, 122.5, 117.1, 116.8, 68.0 ppm. MS (EI) m/z 226 (M^+). Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N 12.38; Found: C, 68.81; H, 4.52; N 12.15.

2-Methyl-4-phenyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3i). A white solid; Mp 78–80 °C; IR (neat) ν_{max}/cm^{-1} 3037.1, 2937.5, 1688.7, 1591.3, 1491.0, 1367.9, 1266.0, 1107.5 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.54–7.50 (m, 2H), 7.46–7.42 (m, 1H), 7.27–7.24 (m, 2H), 7.04 (dd, J = 8.4, 1.2 Hz, 1H), 7.00–6.98 (m, 1H), 6.86–6.82(m, 1H), 6.41 (d, J = 8.0 Hz, 1H), 4.80 (q, J = 6.8 Hz, 1H), 1.65 (d, J = 6.8 Hz, 3H) ppm.^{13}C NMR (100 MHz, $CDCl_3$/TMS): 166.6, 144.1, 136.3, 130.8, 129.9, 128.7, 128.6, 124.0, 122.3, 117.2, 117.0, 73.9, 16.3 ppm. MS (EI) m/z 239 (M^+). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85; Found: C, 75.51; H, 5.36; N, 5.98.

4-Butyl-2-ethyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3j). A colorless oil; IR (neat) ν_{max}/cm^{-1} 3073.3, 2961.1, 1678.5, 1606.2, 1499.2, 1398.4, 1272.4, 1048.3 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.01–6.95 (m, 4H), 4.46 (q, J = 4.0 Hz, 1H), 3.97–3.85 (m, 2H), 1.95–1.81 (m, 2H), 1.67–1.60 (m, 2H), 1.45–1.35 (m, 2H), 1.07 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 166.0, 144.1, 128.5, 123.5, 122.3, 117.4, 114.5, 78.1, 41.0, 29.1, 23.6, 20.0, 13.7, 9.4 ppm. MS (EI) m/z 233 (M^+). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00; Found: C, 72.28; H, 8.32; N, 6.11.

6-*tert*-Butyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3k). A white solid;[10e] Mp 150–151 °C; IR (neat) ν_{max}/cm^{-1} 3568.0, 3092.3, 2963.9, 1692.9, 1605.2, 1492.8, 1387.8, 1207.3, 1039.0 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 9.15 (s, 1H), 7.00 (dd, J = 8.4, 2.4 Hz 1H), 4.58 (s, 2H), 3.92 (t, J = 7.6 Hz, 2H), 1.69–1.61 (m, 2H), 1.46–1.36 (m, 2H), 0.96(t, J = 7.6 Hz, 3H) ppm.^{13}C NMR (100 MHz, $CDCl_3$/TMS): 166.4, 146.1, 141.3, 125.4, 121.0, 116.0, 113.1, 67.2, 34.3, 31.3 ppm.

6-Methyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3l). A white solid;[10f] Mp 205–207 °C; IR (neat) ν_{max}/cm^{-1} 3504.6, 3103.9, 2976.1, 1697.2, 1604.3, 1491.2, 1400.3, 1218.8, 1043.6 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 9.01 (s, 1H), 6.86 (d, J = 8.0 Hz 1H), 6.78 (dd, J = 8.0, 1.2 Hz 1H), 6.64 (d, J = 1.2 Hz, 1H), 4.60 (s, 2H), 2.28 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6/TMS): 170.2, 146.0, 136.7, 131.4, 128.4, 121.3, 120.6, 71.9, 25.3 ppm.

6-Chloro-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3m). A light yellow solid;[10g] Mp 180–182 °C; IR (neat) ν_{max}/cm^{-1} 3505.4, 3127.8, 2959.1, 1696.9, 1603.6, 1492.0, 1395.6, 1212.9, 1042.7 cm^{-1}. ^{1}H

NMR (400 MHz, $CDCl_3$/TMS): δ 8.58 (s, 1H), 6.95 (dd, $J = 9.2$, 2.4 Hz, 1H), 6.91 (d, $J = 9.2$ Hz, 1H), 6.83 (d, $J = 2.4$ Hz, 1H), 4.62 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6/TMS): 169.6, 146.9, 133.2, 131.5, 127.4, 122.1, 120.6, 71.8 ppm.

6-*tert*-Butyl-4-phenyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3n). A white solid; Mp 116–118 °C; IR (neat) ν_{max}/cm^{-1} 3060.3, 2962.2, 1695.1, 1604.6, 1507.5, 1360.3, 1280.2, 1046.4 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.56–7.52 (m, 2H), 7.48–7.45 (m, 1H), 7.31–7.30 (m, 2H), 7.01 (dd, $J = 8.8$, 2.4 Hz 1H), 6.96 (d, $J =$ 8.4 Hz, 1H), 6.43 (d, $J = 2.0$ Hz, 1H), 4.75 (s, 2H), 1.12 (s, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 164.4, 145.2, 142.7, 136.3, 130.4, 130.2, 129.3, 129.0, 120.8, 116.5, 113.4, 68.0, 34.3, 31.3 ppm. MS (EI) *m*/*z* 281 (M$^+$). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98; Found: C, 77.05; H, 6.90; N, 5.12.

6-Methyl-4-phenyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3o). A white solid; Mp 112–114 °C; IR (neat) ν_{max}/cm^{-1} 3053.3, 2917.5, 1689.8, 1589.7, 1510.7, 1366.0, 1272.9, 1055.0 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.57–7.53 (m, 2H), 7.49–7.46 (m, 1H), 7.30–7.26 (m, 2H), 6.93 (d, $J = 7.6$ Hz, 1H), 6.79 (d, $J =$ 8.0 Hz, 1H), 6.21 (s, 1H), 4.74 (s, 2H), 2.15 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 164.5, 142.7, 135.8, 132.3, 130.3, 130.0, 128.8, 128.7, 124.5, 117.3, 116.7, 68.2, 20.9 ppm. MS (EI) *m*/*z* 239 (M$^+$). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85; Found: C, 75.21; H, 5.56; N, 5.68.

6-Chloro-4-phenyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3p). A light yellow solid; Mp 112–114 °C; IR (neat) ν_{max}/cm^{-1} 3079.3, 2922.7, 1687.1, 1598.1, 1492.1, 1363.4, 1260.2, 1055.8 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_{3\,3}$/TMS): δ 7.58–7.54 (m, 2H), 7.51–7.48 (m, 1H), 7.27 (d, $J = 7.6$ Hz, 2H), 6.99–6.92 (m, 2H), 6.40 (d, $J = 1.5$ Hz, 1H), 4.76 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 163.9, 143.4, 135.1, 131.5, 130.2, 129.2, 128.5, 127.6, 123.7, 118.0, 116.7, 68.0 ppm. MS (EI) *m*/*z* 259 (M$^+$). Anal. Calcd for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39; Found: C, 64.44; H, 3.77; N, 5.18.

6-*tert*-Butyl-4-butyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3q). A colorless oil; IR (neat) ν_{max}/cm^{-1} 3073.3, 2958.1, 1683.7, 1608.0, 1514.8, 1437.1, 1382.1, 1276.1, 1047.9 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.02–7.00 (m, 2H), 6.91 (d, $J = 8.4$ Hz, 1H), 4.56 (s, 2H), 3.96 (t, $J = 7.6$ Hz, 2H), 1.70–1.63 (m, 2H), 1.48–1.38 (m, 2H), 1.32 (s, 9H), 0.99 (t, $J = 7.2$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 164.3, 148.7, 143.0, 127.8, 120.4, 116.3, 112.0, 67.6, 40.5, 34.4, 31.4, 29.0, 20.0, 13.7 ppm. MS (EI) *m*/*z* 261 (M$^+$). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36; Found: C, 73.31; H, 8.18; N, 5.16.

6-Methyl-4-butyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3r). A colorless oil;[10h] IR (neat) ν_{max}/cm^{-1} 3047.5, 2928.4, 1681.3, 1609.5, 1511.3, 1439.3, 1382.4, 1274.1, 1048.9 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 6.87 (d, $J = 8.4$ Hz, 1H), 6.79 (d, $J = 6.8$ Hz, 1H), 4.55 (s, 2H), 3.91 (t, $J = 7.2$ Hz, 2H), 2.34 (s, 3H), 1.68–1.61 (m, 2H), 1.46–1.37 (m, 2H), 0.97 (t, $J = 7.2$ Hz, 3H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 164.4, 143.1, 132.2, 128.2, 124.0, 116.7, 115.4, 67.6, 40.7, 29.1, 21.1, 20.0, 13.7 ppm.

6-Chloro-4-butyl-2-ethyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3s). A light yellow solid; Mp 45–47 °C; IR (neat) ν_{max}/cm^{-1} 3079.6, 2954.4, 1677.3, 1603.8, 1494.8, 1433.5, 1351.2, 1255.1, 1116.2 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 6.96–6.90 (m, 3H), 4.45 (q, $J = 4.4$ Hz, 1H), 3.93–3.81 (m, 2H), 1.96–1.77 (m, 2H), 1.68–1.59 (m, 2H), 1.45–1.36 (m, 2H), 1.06 (t, $J = 7.2$ Hz, 3H), 0.97 (t, $J = 7.2$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 165.7, 142.7, 129.6, 127.3, 123.2, 118.3, 114.6, 78.1, 41.1, 29.0, 23.6, 19.9, 13.7, 9.3 ppm. MS (EI) *m*/*z* 267 (M$^+$). Anal. Calcd for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; N, 5.23; Found: C, 63.11; H, 6.71; N, 5.01.

6-Fluoro-2-methyl-4-phenyl-(2*H*)-1,4-benzoxazin-3(4*H*)-one (3t). A light yellow solid; Mp 96–98 °C; IR (neat) ν_{max}/cm^{-1} 3079.3, 2924.6, 1694.4, 1597.1, 1498.1, 1367.1, 1250.8, 1105.3 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.56–7.45 (m, 3H), 7.26 (d, $J = 6.8$ Hz, 1H), 6.98 (dd, $J = 8.8$, 4.8 Hz, 1H), 6.70–6.65 (m, 1H), 6.15 (dd, $J = 9.6$, 3.2 Hz, 1H), 4.77 (q, $J = 6.8$ Hz, 1H), 1.64 (d, $J = 6.8$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$/TMS): 166.5, 157.9 (d, $J_{CF} = 238.9$ Hz, 1C), 140.1 (d, $J_{CF} = 2.4$ Hz, 1C), 135.8, 130.7 (d, $J_{CF} = 10.2$ Hz, 1C), 130.1, 129.0, 128.5, 117.9 (d, $J_{CF} = 9.2$ Hz, 1C), 109.9 (d, $J_{CF} = 22.4$ Hz, 1C), 104.2 (d, $J_{CF} =$ 29.4 Hz, 1C), 73.9, 16.1 ppm. MS (EI) *m*/*z* 257 (M$^+$). Anal. Calcd for $C_{15}H_{12}FNO_2$: C, 70.03; H, 4.70; N, 5.44; Found: C, 71.15; H, 4.78; N, 5.23.

Acknowledgements

This work was financially supported by the Natural Science Foundation of China (No. 20572095) and the Specialized Research Fund for the Doctoral Program Foundation of Higher Education of China (No. 2060335036).

References

1 For recent reviews, see: (*a*) B. Achari, S. B. Mandal, P. K. Dutta and C. Chowdhury, *Synlett*, 2004, 2449; (*b*) J. Ilaš, P.Š t. Anderluh, M. S. Dolenc and D. Kikelj, *Tetrahedron*, 2005, **61**, 7325.

2 (*a*) H. M. Niemeyer, *Phytochemistry*, 1988, **27**, 3349; (*b*) Y. Minami, K. Yosa, R. Azuma, M. Saeki and T. Otani, *Tetrahedron Lett.*, 1993, **34**, 2633; (*c*) W. M. Dai, *Curr. Med. Chem.*, 2003, **10**, 2265; (*d*) H. Tsutsui, M. Hori, I. Watanabe, K. Harada, J. Maruo, T. Morita, H. Ohtaka, T. Yamamoto, EP Patent Appl. 719766, 1996; (*e*) R. Frechette and M. A. Weidner-Wells, WO Patent Appl. 9717333, 1997; (*f*) G. F. Feng, J. L. Wu and W.-M. Dai, *Tetrahedron*, 2006, **62**, 4635.

3 (*a*) P. J. Rybczynski, R. E. Zeck, J. Dudash, D. W. Combs, T. P. Burris, M. Yang, M. C. Osborne, X. l. Chen and K. T. Demarest, *J. Med. Chem.*, 2004, **47**, 196; (*b*) A. Arrault, F. Touzeau, G. Guillaumet, J. M. Le'ger, C. Jarry and J. Y. Me'rour, *Tetrahedron*, 2002, **58**, 8145; (*c*) G. Caliendo, E. Perissutti, V. Santagada, F. Fiorino, B. Severino, D. Cirillo, R. d'Emmanuele di Villa Bianca, L. Lippolis, A. Pinto and R. Sorrentino, *Eur. J. Med. Chem.*, 2004, **39**, 815; (*d*) T. Kuroita, N. Marubayashi, M. Sano, K. Kanzaki, K. Inaba and T. Kawakita, *Chem. Pharm. Bull*, 1996, **44**, 2051.

4 (*a*) W. M. Dai, X. Wang and C. Ma, *Tetrahedron*, 2005, **61**, 6879; (*b*) X. L. Xing, J. L. Wu, G. F. Feng and W. M. Dai, *Tetrahedron*, 2006, **62**, 6774.

5 For recent reviews on copper-catalyzed *N*-arylation, see: (*a*) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428; (*b*) S. V. Ley and A. W. Thomas, *Angew. Chem.*, 2003, **115**, 5558; S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*c*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; (*d*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054.

6 (*a*) X. LV, Y. Y. Liu, W. X. Qian and W. L. Bao, *Adv. Synth. Catal.*, 2008, **350**, 2507; (*b*) W. L. Bao, Y. Y. Liu, X. LV and W. X. Qian, *Org. Lett.*, 2008, **10**, 3899; (*c*) D. S. Yang, H. Fu, L. M. Hu, Y. Y. Jiang and Y. F. Zhao, *J. Org. Chem.*, 2008, **73**, 7841; (*d*) X. W. Liu, H. Fu, Y. Y. Jiang and Y. F. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 348; (*e*) F. S. Melkonyan, A. V. Karchava and M. A. Yurovskaya, *J. Org. Chem.*, 2008, **73**, 4275–4278; (*f*) Q. L. Yuan and D. W. Ma, *J. Org. Chem.*, 2008, **73**, 5159.

7 X. Lv and W. L. Bao, *J. Org. Chem.*, 2007, **72**, 3863.
8 F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2003, **5**, 793.
9 4-Substituted-*o*-iodophenols have been synthesized; see: (*a*) J. Edgar and S. N. Falling, *J. Org. Chem.*, 1990, **55**, 5287. *N*-Substituted 2-haloamides have been synthesized; see: (*b*) M. Y. Chang, S. T. Chen and N. C. Chang, *Tetrahedron*, 2002, **58**, 3623; (*c*) P. G. Baraldi, D. Preti, M. A. Tabrizi, F. Fruttarolo, G. Saponaro, S. Baraldi, R. Romagnoli, A. R. Moorman, A. Gessi, K. Varani and P. A. Barea, *Bioorg. Med. Chem.*, 2007, **15**, 2514.
10 (*a*) K. Rüfenacht, H. Kristinsson and G. Mattern, *Helv. Chim. Acta*, 1976, **59**, 1593; (*b*) H. L. Roche, US 1951807, 1932; (*c*) A. R. Forrester, J. Skilling and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2161; (*d*) E. G. Feng, H. Huang, Y. Zhou, D. J. Ye, H. L. Jiang and H. Liu, *J. Org. Chem.*, 2009, **74**, 2846; (*e*) D. J. Drain, M. J. Daly, B. Davy, M. Horlington, J. G. Howes, J. M. Scruton and R. A. Selway, *J. Pharm. Pharmacol.*, 1970, **22**, 684; (*f*) K. L. Kirk and L. A. Cohen, *J. Am. Chem. Soc.*, 1972, **94**, 8142; (*g*) H. Yuichi, I. Takayoshi, S. Koichi and O. Toshihiko, *Chem. Pharm. Bull.*, 1983, **31**, 3891; (*h*) D. L. Giampiero, WO Pat. Appl. 2004006916, 2004.
11 While this manuscript was being prepared, a similar reaction using microwave-assisted methods by Feng *et al.* appeared on the web, see ref. 10d.