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SYNTHESIS OF 2-ARYL-(*Z*)-4-(HALOMETHYLIDENE)-4*H*-3,1-BENZOXAZINES BY SODIUM HYDRIDE MEDIATED CYCLIZATION OF *N*-[2-(2,2-DIHALOETHENYL)PHENYL]ARENECARBOXAMIDES

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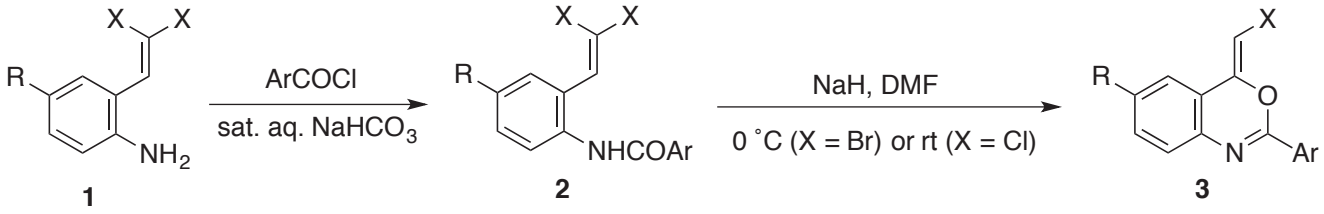
Abstract – A simple two-step procedure for the preparation of 2-aryl-(*Z*)-4-(halomethylidene)-4*H*-3,1-benzoxazines from readily available 2-(2,2-dihaloethenyl)benzenamines is developed. Thus, these amines were *N*-aroylated with the respective aroyl chloride to give *N*-[2-(2,2-dihaloethenyl)phenyl]arenecarboxamides, which in turn were treated with sodium hydride to afford the desired products.

INTRODUCTION

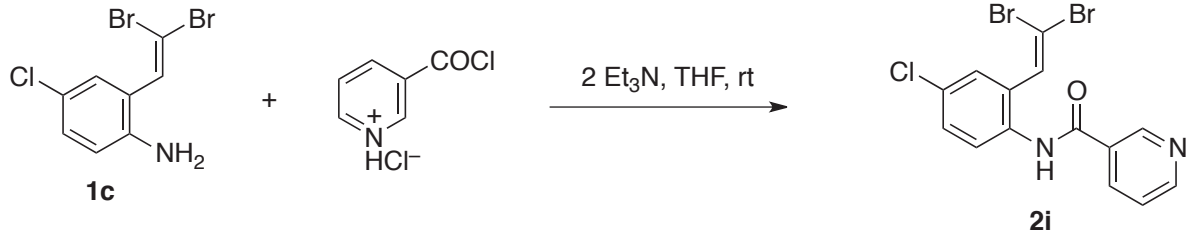
As 4-alkylidene-4*H*-3,1-benzoxazine derivatives are of synthetically importance, a number of methods for the preparation of this class of molecules have recently been reported.[1,2] On the other hand, our previous study has shown that 2-(2,2-dihaloethenyl)phenyl isothiocyanates were easily prepared from the respective 2-(2,2-dihaloethenyl)benzenamines and that the corresponding thiourea derivatives, derived from these isothiocyanates and secondary amines, underwent ring closure on treatment with sodium hydride to result in the stereoselective formation of *N*,*N*-disubstituted (*Z*)-4-(halomethylidene)-4*H*-3,1-benzothiazin-2-amines.[3] So, we became interested in the possibility of extending this type of ring closure for the construction of the (*Z*)-4-(halomethylidene)-4*H*-3,1-benzoxazine structure. In this paper, we wish to report a simple approach to (*Z*)-4-(halomethylidene)-2-(het)aryl-4*H*-3,1-benzoxazines (**3**) from 2-(2,2-dihaloethenyl)benzenamines (**1**), which involves the *N*-(het)aroylation of **1** with (het)aroyl chlorides and subsequent treatment of the resulting amides (**2**) with sodium hydride under mild conditions. We also demonstrate α-hydroxyalkylation on the carbon adjacent to the chloro atom of a 4-(chloromethylidene) derivative.

RESULTS AND DISCUSSION

The synthesis of 4*H*-3,1-benzoxazine derivatives (**3**) was conducted according to the sequence illustrated in Scheme 1. *N*-[2-(2,2-Dihaloethenyl)phenyl](het)arenecarboxamides (**2**), excluding **2i**, were prepared by the reaction of 2-(2,2-dihaloethenyl)benzenamines (**1**), readily obtainable from commercially available 2-nitrobenzaldehydes according to the appropriate reported procedures,[4-7] with (het)aroyl chlorides in saturated aqueous sodium hydrogencarbonate at room temperature. The pyridine-3-carboxamide derivative (**2i**) could be obtained by *N*-(pyridine-3-carbonyl)ation of **1c** with pyridine-3-carbonyl chloride hydrochloride in THF in the presence of two equivalents of triethylamine at room temperature (Scheme 2). In each case, the yield of the product was good as compiled in Table 1.



Scheme 1



Scheme 2

Table 1. Preparation of (*Z*)-4-(halomethylidene)-4*H*-3,1-benzoxazines (**3**)

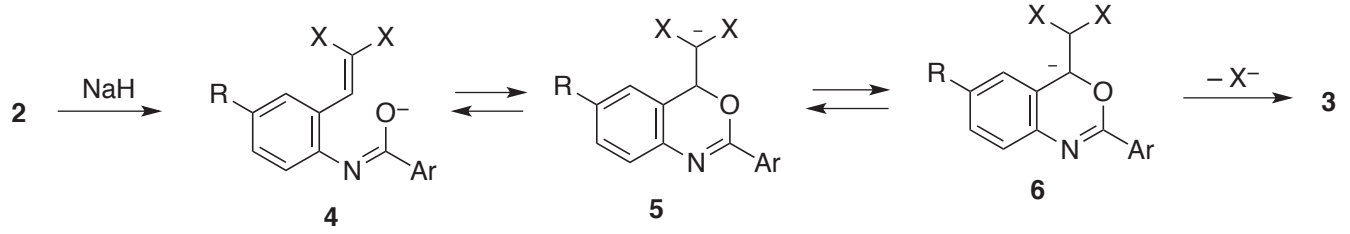
Entry	**1**	Ar	**2**	Yield/%[a]	**3**	Yield/%[a]
1	**1a** (R = H, X = Br)	Ph	**2a**	76	**3a**	76
2	**1a**	3-MeC_6H_4	**2b**	82	**3b**	69
3	**1a**	4-ClC_6H_4	**2c**	79	**3c**	77
4	**1a**	3-$MeOC_6H_4$	**2d**	82	**3d**	76
5	**1b** (R = H, X = Cl)	Ph	**2e**	79	**3e**	86
6	**1b**	thiophen-2-yl	**2f**	77	**3f**	69
7	**1c** (R = Cl, X = Br)	Ph	**2g**	72	**3g**	73
8	**1c**	3-ClC_6H_4	**2h**	66	**3h**	81
9	**1c**	pyridin-3-yl	**2i**	67	**3i**	71
10	**1d** (R = OMe, X = Br)	Ph	**2j**	82	**3j**	71
11	**1d**	4-ClC_6H_4	**2k**	83	**3k**	73

[a] Yields of isolated products.

These amides (**2**), thus obtained, were subsequently transformed into the corresponding desired (*Z*)-4-(halomethylidene)-4*H*-3,1-benzoxazine derivatives (**3**) in generally good yields on treatment with sodium hydride in DMF. These results are also compiled in Table 1. While the ring closure sequence of the 2,2-dibromoethenyl substrates proceeded very smoothly at 0 ˚C, that of the 2,2-dichloroethenyl substrate was reluctant at 0 ˚C and room temperature was required for an adequate progress and satisfactory production of the desired products. The ring closure sequence proceeded with complete stereoselectivity to give **3**. Entry 9 shows that cyclization of pyridine-3-carboxamide precursor **2i** under the same conditions gave also the corresponding desired product **3i** in a yield comparable to the others. Each of these products could be isolated in a pure form by recrystallization after usual aqueous workup. The stereochemistry of the 4-halomethylidene unit of each product was assigned to be *Z* on the basis of NOESY analyses of the products. For example, an interaction between the vinyl proton (δ 5.97) and 5-proton (δ 7.35) of **3g** was observed. The exclusive formation of *Z*-isomer is due to the avoidance of the steric repulsion between the halogen atom and 5-H.

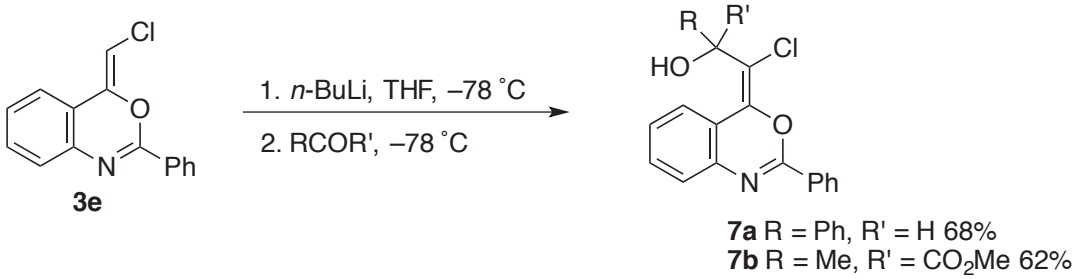
It is notable that all attempts to prepare 2-alkyl-4-(halomethylidene)-4*H*-3,1-benzoxazine derivatives from *N*-[2-(2,2-dihaloethenyl)phenyl]alkanamides under the same conditions as described above resulted in the formation of complex reaction mixtures. The corresponding desired products are thought to be unstable under reaction and/or work-up conditions.

The formation of **3** from **2** probably proceeds in an analogous manner to that indicated previously for the formation of *N,N*-disubstituted (*Z*)-4-(halomethylidene)-4*H*-3,1-benzothiazin-2-amines from the respective thiourea derivatives, derived from 2-(2,2-dihaloethenyl)phenyl isothiocyanates and secondary amine.[3] As illustrated in Scheme 3, deprotonation of the amide NH hydrogen of **2** with sodium hydride gave the imidate anion intermediate **4**. Then, attack of the oxy anion on the β-position of the dihalovinyl function gives α,α-dihalo carbanion intermediate **5**. Proton transfer gives the benzyl anion intermediate **6**, from which a halide anion is eliminated to give rise to **3**. Thus, the slow production of **3** with X = Cl is indicative of the fact that the corresponding intermediates **5** with X = Cl are more stable than that with X = Br.



Scheme 3

In order to demonstrate the synthetic utility of these novel compounds (**3**), we next explored the reaction of **3a** and **3e** with butyllithium. When **3a** was successively treated with butyllithium and benzaldehyde in THF at –78 ˚C, an inseparable mixture of the products including those arising from the lithiation at the vinyl carbon and the bromine/lithium exchange was obtained after aqueous workup. In the case of **3e**, the lithiation at the vinyl carbon took place selectively, and the resulting lithium compound reacted with carbonyl compounds, such as benzaldehydes and methyl 2-oxopropanoate, to afford the corresponding desired products **7** in fair yields, as shown in Scheme 4.



Scheme 4

In conclusion, the present study has led to the development of a convenient method for the preparation of a new type of 4*H*-3,1-benzoxazines, (*Z*)-4-(halomethylidene)-2-(het)aryl-4*H*-3,1-benzoxazines. Simple manipulations as well as the readily availability of the starting materials make it attractive. Investigations of possibility of utilizing these 4*H*-3,1-benzoxazine derivatives for elaboration to the other heterocyclic systems are presently under way in our laboratory.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded as KBr discs, unless otherwise stated, with a Perkin–Elmer Spectrum65 FTIR spectrophotometer. ^{1}H NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or Bruker Biospin AVANCE II 600 FT NMR spectrometer at 600 MHz. ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. High-resolution MS spectra were measured by a Thermo Scientific Exactive spectrometer. Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 2-(2,2-Dihaloethenyl)benzenamines **1a**,[4] **1b**,[5] **1c**,[6] and **1d**[7] were prepared according to the appropriate reported procedures. *n*-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of *N*-[2-(2,2-Dihaloethenyl)phenyl]benzamides (2), Excluding 2i. *N*-[2-(2,2-Dibromoethenyl)phenyl]benzamide (2a).[8] To a stirring mixture of **1a** (0.22 g, 0.81 mmol) in saturated aqueous $NaHCO_3$ (8 mL) at rt was added BzCl (0.13 g, 0.89 mmol) dropwise. After 1 h, AcOEt (10 mL) was added and the layers were separated. The aqueous layer was extracted with AcOEt (2 × 5 mL) and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized from hexane/CH_2Cl_2 to give **2a** (0.24 g, 76%); a white solid; mp 111–112 °C; IR 3235, 1647 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.4 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.44 (dd, *J* = 8.6, 7.4 Hz, 1H), 7.50 (s, 1H), 7.54 (t, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.78 (br, 1H), 7.89 (d, *J* = 7.4 Hz, 2H), 8.16 (d, *J* = 8.6 Hz, 1H).

***N*-[2-(2,2-Dibromoethenyl)phenyl]-3-methylbenzamide (2b):** a white solid; mp 103–104 °C (hexane/CH_2Cl_2); IR 3241, 1647 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.38–7.45 (m, 4H), 7.50 (s, 1H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.71 (br s, 1H), 7.78 (br, 1H), 8.15 (d, *J* = 8.4 Hz, 1H). Anal. Calcd for $C_{16}H_{13}Br_2NO$: C, 48.64; H, 3.32; N, 3.55. Found: C, 48.59; H, 3.41; N, 3.42.

4-Chloro-*N*-[2-(2,2-dibromoethenyl)phenyl]benzamide (2c): a white solid; mp 162–164 °C (hexane/CH_2Cl_2); IR 3268, 1654 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.48 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.77 (br, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 7.6 Hz, 1H). Anal. Calcd for $C_{15}H_{10}Br_2ClNO$: C, 43.36; H, 2.43; N, 3.37. Found: C, 43.26; H, 2.40; N, 3.19.

***N*-[2-(2,2-Dibromoethenyl)phenyl]-3-methoxybenzamide (2d):** a white solid; mp 105–107 °C (hexane/CH_2Cl_2); IR 3235, 1639 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.11 (tt, *J* = 7.4, 2.3 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.39–7.44 (m, 4H), 7.49 (s, 1H), 7.81 (br, 1H), 8.14 (d, *J* = 8.6 Hz, 1H). Anal. Calcd for $C_{16}H_{13}Br_2NO_2$: C, 46.75; H, 3.19; N, 3.41. Found: C, 46.60; 3.19; N, 3.38.

***N*-[2-(2,2-Dichloroethenyl)phenyl]benzamide (2e):** a white solid; mp 122–125 °C (hexane/CH_2Cl_2); IR 3250, 1647 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1H), 7.23 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.42 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 7.4, 6.9 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.73 (br, 1H), 7.88 (d, *J* = 6.9 Hz, 2H), 8.09 (d, *J* = 8.0 Hz, 1H). Anal. Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.67; H, 3.79; N, 4.79. Found: C, 61.51; 3.89; N, 4.72.

***N*-[2-(2,2-Dichloroethenyl)phenyl]thiophene-2-carboxamide (2f):** a white solid; mp 130–132 °C (hexane/CH_2Cl_2); IR 3245, 1630, 1600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1H), 7.16 (dd, *J* = 5.2, 4.0 Hz, 1H), 7.22 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.40 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H),

7.58 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.60 (br, 1H), 7.62 (dd, *J* = 4.0, 1.1 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H). Anal. Calcd for $C_{13}H_9Cl_2NOS$: C, 52.36; H, 3.04; N, 4.70. Found: C, 52.39; 3.04; N, 4.49.

***N*-[4-Chloro-2-(2,2-dibromoethenyl)phenyl]benzamide (2g):** a white solid; mp 151–153 ˚C (hexane/CH_2Cl_2); IR 3234, 1648, 1603 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.3 Hz, 1H), 7.39 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.43 (s, 1H), 7.54 (t, *J* = 7.4 Hz, 2H), 7.60 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.74 (br, 1H), 7.87 (7.4, 1.1 Hz, 2H), 8.14 (d, *J* = 8.6 Hz, 1H). Anal. Calcd for $C_{15}H_{10}Br_2ClNO$: C, 43.36; H, 2.43; N, 3.37. Found: C, 43.36; 2.47; N, 3.39.

3-Chloro-*N*-[4-Chloro-2-(2,2-dibromoethenyl)phenyl]benzamide (2h): a white solid; mp 159–160 ˚C (hexane/CH_2Cl_2); IR 3278, 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.3 Hz, 1H), 7.40 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.43 (s, 1H), 7.47 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.57 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.69 (br, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.87 (t, *J* = 1.1 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 1H). Anal. Calcd for $C_{15}H_9Br_2Cl_2NO$: C, 40.04; H, 2.02; N, 3.11. Found: C, 40.06; 2.04; N, 3.04.

***N*-[4-Chloro-2-(2,2-dibromoethenyl)phenyl]pyridine-3-carboxamide (2i).** To a stirred mixture of **1c** (0.22 g, 0.71 mmol) and pyridine-3-carbonyl chloride hydrochloride (0.14 g, 0.78 mmol) in THF (3 mL) at rt was added Et_3N (0.18 g, 1.8 mmol), and stirring was continued overnight at the same temperature. Saturated aqueous $NaHCO_3$ (15 mL) was added, and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with water (3 × 10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated by evaporation. The residue was purified by column chromatography on silica gel to afford **2i** (0.15 g, 67%); a pale-yellow viscous oil; R_f 0.25 (AcOEt/hexane 5:1); IR (neat) 3251, 1656 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.41 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.44 (s, 1H), 7.49 (dd, *J* = 8.0, 4.6 Hz, 1H), 7.76 (br, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.82 (d, *J* = 4.6 Hz, 1H), 9.10 (s, 1H). Anal. Calcd for $C_{14}H_9Br_2ClN_2O$: C, 40.37; H, 2.18; N, 6.73. Found: C, 40.39; 2.23; N, 6.77.

***N*-[2-(2,2-Dibromoethenyl)-4-methoxyphenyl]benzamide (2j):** a white solid; mp 127–130 ˚C (hexane/CH_2Cl_2); IR 3235, 1640, 1619, 1602 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.95–6.98 (m, 2H), 7.47 (s, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.62 (br, 1H), 7.85–7.88 (m, 3H). Anal. Calcd for $C_{16}H_{13}Br_2NO_2$: C, 46.75; H, 3.19; N, 3.41. Found: C, 46.70; 3.39; N, 3.36.

4-Chloro-*N*-[2-(2,2-dibromoethenyl)-4-methoxyphenyl]benzamide (2k): a pale-yellow solid; mp 156–158 ˚C (hexane/CH_2Cl_2); IR 3244, 1647 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.94–6.97 (m, 2H), 7.45 (s, 1H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.57 (br, 1H), 7.79–7.83 (m, 3H). Anal. Calcd for $C_{16}H_{12}Br_2ClNO_2$: C, 43.13; H, 2.71; N, 3.14. Found: C, 43.05; 2.76; N, 3.02.

General Procedure for the Preparation of 2-Aryl-(Z)-4-(halomethylidene)-4*H*-1,3-benzoxazines (3). To a stirred solution of **2** (1.0 mmol) in DMF (5 mL) at 0 ˚C was added NaH (60% in mineral oil; 47 mg, 1.2 mmol) in several portions. The mixture was stirred at the same temperature (for X = Br) or rt (for X = Cl), until complete consumption of the starting material (TLC on silica gel; about 5 h for X =Br and

overnight for X = Cl). Water (20 mL) was then added and the resulting mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with water (3 × 10 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized from hexane/CH_2Cl_2 to give **3**.

(*Z*)-4-(Bromomethylidene)-2-phenyl-4*H*-1,3-benzoxazine (3a). a pale-yellow solid; mp 105–107 °C; IR 1645, 1612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 7.23 (td, *J* = 7.6, 2.3 Hz, 1H), 7.36–7.42 (m, 3H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.55 (tt, *J* = 7.6, 1.5 Hz, 1H), 8.28 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.79, 119.90, 121.72, 126.90, 127.84, 128.02, 128.45, 130.82, 131.04, 132.01, 138.24, 147.68, 154.12. HR-MS (DART, positive). Calcd for $C_{15}H_{11}BrNO$ (M+H): 300.0024. Found: *m/z* 300.0017. Anal. Calcd for $C_{15}H_{10}BrNO$: C, 60.02; H, 3.36; N, 4.67. Found: C, 59.98; H, 3.61; N, 4.63.

(*Z*)-4-(Bromomethylidene)-2-(3-methylphenyl)-4*H*-1,3-benzoxazine (3b): a pale-yellow solid; mp 131–133 °C ; IR 1644, 1613 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.45 (s, 3H), 5.96 (s, 1H), 7.21 (td, *J* = 7.5, 1.6 Hz, 1H), 7.36–7.40 (m, 5H), 8.08 (d, *J* = 9.2 Hz, 1H), 8.09 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.50, 79.76, 119.95, 121.76, 125.27, 126.89, 127.82, 128.42, 128.57, 130.78, 131.08, 132.92, 128.22, 138.35, 147.76, 154.40. HR-MS (DART, positive). Calcd for $C_{16}H_{13}BrNO$ (M+H): 314.0180. Found: *m/z* 314.0179. Anal. Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46. Found: C, 61.17; H, 4.01; N, 4.43.

(*Z*)-4-(Bromomethylidene)-2-(4-chlorophenyl)-4*H*-1,3-benzoxazine (3c): a pale-yellow solid; mp 179–182 °C ; IR 1646, 1613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (s, 1H), 7.23 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.33–7.40 (m, 3H), 7.45 (d, *J* = 8.0 Hz, 2H), 8.20 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 80.06, 119.89, 121.75, 126.94, 128.06, 128.78, 129.35, 131.13 (2 overlapped Cs), 138.05, 138.29, 147.61, 153.24. HR-MS (DART, positive). Calcd for $C_{15}H_{10}BrClNO$ (M+H): 333.9634. Found: *m/z* 333.9624. Anal. Calcd for $C_{15}H_9BrClNO$: C, 53.84; H, 2.71; N, 4.19. Found: C, 53.55; 2.85; N, 4.08.

(*Z*)-4-(Bromomethylidene)-2-(3-methoxyphenyl)-4*H*-1,3-benzoxazine (3d): a pale-yellow solid; mp 113–115 °C ; IR 1641, 1615 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3H), 5.96 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.22 (dd, *J* = 8.0, 6.9 Hz, 1H), 7.36–7.41 (m, 4H), 7.82 (s, 1H), 7.88 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.40, 79.80, 112.47, 118.63, 119.95, 120.58, 121.73, 126.94, 127.89, 129.50, 131.04, 132.18, 138.25, 147.70, 153.97, 159.61. HR-MS (ESI, positive). Calcd for $C_{16}H_{13}BrNO_2$ (M+H): 330.0129. Found: *m/z* 330.0119. Anal. Calcd for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; N, 4.24. Found: C, 58.06; 3.86; N, 4.12.

(*Z*)-4-(Chloromethylidene)-2-phenyl-4*H*-1,3-benzoxazine (3e): a pale-yellow solid; mp 100–101 °C ; IR 1638, 1612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 7.22 (td, *J* = 8.0, 1.7 Hz, 1H), 7.37–7.39 (m, 3H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.55 (dd, *J* = 7.4, 6.9 Hz, 1H), 8.27 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 92.52, 119.43, 121.12, 126.93, 127.75, 128.00, 128.44, 130.89, 130.93, 131.98, 138.23, 146.22,

153.99. HR-MS (ESI, positive). Calcd for $C_{15}H_{11}ClNO$ (M+H): 256.0529. Found: *m*/*z* 256.0523. Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.32; 3.91; N, 5.41.

(*Z*)-4-(Chloromethylidene)-2-(thiophen-2-yl)-4*H*-1,3-benzoxazine (3f): a pale-yellow solid; mp 114–116 ˚C ; IR 1639, 1611 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.94 (s, 1H), 7.14 (dd, *J* = 5.2, 3.4 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.30–7.37 (m, 3H), 7.54 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.90 (dd, *J* = 3.4, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 92.67, 119.22, 121.20, 126.60, 127.52, 127.91, 130.88, 130.94, 131.16, 134.85, 138.15, 146.07, 150.76. HR-MS (DART, positive). Calcd for $C_{13}H_9ClNOS$ (M+H): 262.0093. Found: *m*/*z* 262.0086. Anal. Calcd for $C_{13}H_8ClNOS$: C, 59.66; H, 3.08; N, 5.35. Found: C, 59.33; H, 3.26; N, 5.18.

(*Z*)-4-(Bromomethylidene)-6-chloro-2-phenyl-4*H*-1,3-benzoxazine (3g): a pale-yellow solid; mp 173–175 ˚C ; IR 1641, 1612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 7.32 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.35 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.0, 6.9 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 81.16, 121.20, 121.63, 128.07, 128.24, 128.50, 130.50, 131.09, 132.22, 133.19, 136.92, 146.62, 154.34. HR-MS (DART, positive). Calcd for $C_{15}H_{10}BrClNO$ (M+H): 333.9634. Found: *m*/*z* 333.9626. Anal. Calcd for $C_{15}H_9BrClNO$: C, 53.84; H, 2.71; N, 4.19. Found: C, 53.58; H, 2.81; N, 4.14.

(*Z*)-4-(Bromomethylidene)-6-chloro-2-(3-chlorophenyl)-4*H*-1,3-benzoxazine (3h): a pale-yellow solid; mp 152–154 ˚C ; IR 1642, 1611 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.32–7.34 (m, 2H), 7.41 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.50 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.10 (dt, *J* = 8.0, 1.1 Hz, 1H), 8.20 (t, *J* = 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 81.59, 121.23, 121.66, 126.09, 128.05, 128.34, 129.77, 131.18, 132.17, 132.27, 133.64, 134.65, 136.51, 146.41, 153.03. HR-MS (DART, positive). Calcd for $C_{15}H_9BrCl_2NO$ (M+H): 367.9244. Found: *m*/*z* 367.9239. Anal. Calcd for $C_{15}H_8BrCl_2NO$: C, 48.82; H, 2.18; N, 3.80. Found: C, 48.60; H, 2.35; N, 3.53.

(*Z*)-4-(Bromomethylidene)-6-chloro-2-(pyridin-3-yl)-4*H*-1,3-benzoxazine (3i): a pale-yellow solid; mp 190–192 ˚C ; IR (KBr) 1645, 1616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.40 (d, *J* = 2.3 Hz, 1H), 7.44 (dd, *J* = 8.0, 5.2 Hz, 1H), 8.49 (dt, *J* = 8.0, 1.7 Hz, 1H), 8.78 (dd, *J* = 5.2, 1.7 Hz, 1H), 9.47 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.90, 121.31, 121.72, 123.26, 126.56, 128.40, 131.23, 133.84, 135.23, 136.30, 146.25, 149.48, 152.58 (two overlapped Cs). HR-MS (DART, positive) Calcd for $C_{14}H_9BrClN_2O$ (M+H): 334.9587. Found: *m*/*z* 334.9580. Anal. Calcd for $C_{14}H_8BrClN_2O$: C, 50.11; H, 2.40; N, 8.35. Found: C, 49.88; H, 2.41; N, 8.30.

(*Z*)-4-(Bromomethylidene)-6-methoxy-2-phenyl-4*H*-1,3-benzoxazine (3j): a yellow solid; mp 141–144 ˚C ; IR 1645, 1611 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.93 (s, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.95 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.32 (8.6 Hz, 1H), 7.46–7.53 (m, 3H), 8.24 (dd, *J* = 6.9, 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.59, 79.70, 105.78, 117.44, 120.60, 127.37, 127.72, 128.30, 128.41, 131.60, 132.06, 147.71, 152.24, 159.02. HR-MS (DART, positive). Calcd for $C_{16}H_{13}BrNO_2$ (M+H): 330.0129.

Found: *m*/*z* 330.0121. Anal. Calcd for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; N, 4.24. Found: C, 58.03; H, 3.74; N, 4.18.

(*Z*)-4-(Bromomethylidene)-2-(4-chlorophenyl)-6-methoxy-4*H*-1,3-benzoxazine (3k): a pale-yellow solid; mp 168–171 ˚C ; IR 1648, 1616 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.92 (s, 1H), 6.83 (d, *J* = 2.9 Hz, 1H), 6.94 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 8.16 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 55.60, 79.96, 105.83, 117.47, 120.56, 128.33, 128.71, 129.00, 129.52, 131.81, 137.82, 147.56, 151.46, 159.16. HR-MS (ESI, positive). Calcd for $C_{16}H_{12}BrClNO_2$ (M+H): 363.9740. Found: *m*/*z* 363.9737. Anal. Calcd for $C_{16}H_{11}BrClNO_2$: C, 52.70; H, 3.04; N, 3.84. Found: C, 52.42; H, 3.09; N, 3.80.

Typical Procedure for the Preparation of Compounds (7). (*Z*)-2-Chloro-1-phenyl-2-(2-phenyl-4*H*-3,1-benzxazin-4-ylidene)ethanol (7a). To a stirred solution of **3e** (0.12 g, 0.46 mmol) in THF (3 mL) at –78 ˚C was added *n*-BuLi (1.6 M in hexane; 0.46 mmol) dropwise. After 10 min, PhCHO (49 mg, 0.46 mmol) was added and stirring was continued for an additional 15 min. Saturated aqueous NH_4Cl (10 mL) was added and temperature was raised to rt. The mixture was extracted with AcOEt (3 × 10 mL) and the combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was purified by recrystallization to afford **7a** (0.11 g, 68%); a lemon-yellow solid; mp 204–206 ˚C (hexane/THF); IR 3224, 1640, 1611 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.06 (s, 1H), 6.32 (s, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.40–7.46 (m, 4H), 7.56–7.59 (m, 3H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.72 (d, *J* = 7.4 Hz, 1H), 8.20 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 69.54, 118.55, 119.44, 125.70, 125.86, 126.12, 127.33, 127.76, 127.92, 128.12, 128.91, 129.94, 131.64, 132.65, 140.31, 141.15, 142.00, 154.71. HR-MS (ESI, positive). Calcd for $C_{22}H_{17}ClNO_2$ (M+H): 362.0948. Found: *m*/*z* 362.0944. Anal. Calcd for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87. Found: C, 72.82; H, 4.35; N, 3.80.

Methyl (*Z*)-3-Chloro-2-hydroxy-2-methyl-3-(2-phenyl-4*H*-3,1-benzoxazin-4-ylidene)propanoate (7b): a yellow solid; mp 148–150 ˚C (hexane/CH_2Cl_2); IR 3280, 1749, 1633 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.83 (s, 3H), 3.37 (s, 3H), 3.59 (s, 1H), 7.26 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.39 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.45 (td, *J* = 7.4, 1.1 Hz, 1H), 7.50 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.55 (tt, *J* = 7.4, 1.7 Hz, 1H), 7.80 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.32 (dd, *J* = 8.6, 1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.63, 53.07, 76.40, 114.66, 119.85, 125.02, 126.63, 127.44, 128.44, 128.49, 130.62, 131.52, 132.16, 140.91, 145.29, 155.78, 174.92. HR-MS (ESI, positive). Calcd for $C_{19}H_{17}ClNO_4$ (M+H): 358.0846. Found: *m*/*z* 358.0838. Anal. Calcd for $C_{19}H_{16}ClNO_4$: C, 63.78; H, 4.51; N, 3.91. Found: C, 63.73; H, 4.63; N, 3.89.

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REFERENCES AND NOTES

1. Transition metal-catalyzed or electrophile-mediated cyclization of *N*-(2-alkynylphenyl)carboxylic amides: (a) M. Costa, N. D. Cà, B. Gabriele, C. Massera, G. Salerno, and M. Soliani, *J. Org. Chem.*, 2004, **69**, 2469; (b) T. Saito, S. Ogawa, N. Takei, N. Katsumura, and T. Otani, *Org. Lett.*, 2011, **13**, 1098; (c) W.-C. Lee, H.-C. Shen, W.-P. Hu, W.-S. Lo, C. Murali, J. K. Vandavasi, and J.-J. Wang, *Adv. Synth. Catal.*, 2013, **354**, 2218; (d) J. K. Vandavasi, K.-K. Kuo, W.-P. Hu, H.-C. Shen, W.-S. Lo, and J.-J. Wang, *Org. Biomol. Chem.*, 2013, **11**, 6520; (e) A. Sinai, A. Mészáros, T. Gáti, V. Kudar, A. Pállo, and Z. Novák, *Org. Lett.*, 2013, **15**, 5654; (f) A. L. Stein, F. N. Bilhert, D. F. Back, and G. Zeni, *Adv. Synth. Catal.,* 2014, **356**, 501.
2. Electrophile-mediated cyclization of 2-isocyanophenyl ketones under non-metallic conditions: (a) K. Kobayashi, Y. Okamura, and H. Konishi, *Synthesis,* 2009, 1494; (b) K. Kobayashi, Y. Okamura, S. Fukamachi, and H. Konishi, *Heterocycles,* 2010, **81**, 1253.
3. K. Kobayashi, K. Yamane, I. Nozawa, and K. Ezaki, *Helv. Chim. Acta,* 2014, **97**, 315.
4. H.-F. He, S. Dong, Y. Chen, Y. Yang, Y. Le, and W. Bao, *Tetrahedron,* 2012, **68**, 3112.
5. Y. Q. Fang and M. Lautens, *J. Org. Chem.*, 2008, **73**, 538.
6. T. O. Vieira, L. A. Meaney, Y.-L. Shi, and H. Alper, *Org. Lett.,* 2008, **10**, 4899.
7. A. R. Kunzer and M. D.Wendt, *Tetrahedron Lett.*, 2011, **52**, 1815.
8. B. Jiang, K. Tao, W. Shen, and J. Zhang, *Tetrahedron Lett.*, 2010, **51**, 6342.