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CONVENIENT SYNTHESIS OF 1,4-DIHYDRO-2*H*-3,1-BENZOXAZIN-2-ONES BY IODOCYCLIZATION OF *t*-BUTYL 2-VINYLPHENYLCARBAMATES

Kazuhiro Kobayashi,* Shuhei Fukamachi, Daizo Nakamura, Osamu Morikawa, and Hisatoshi Konishi

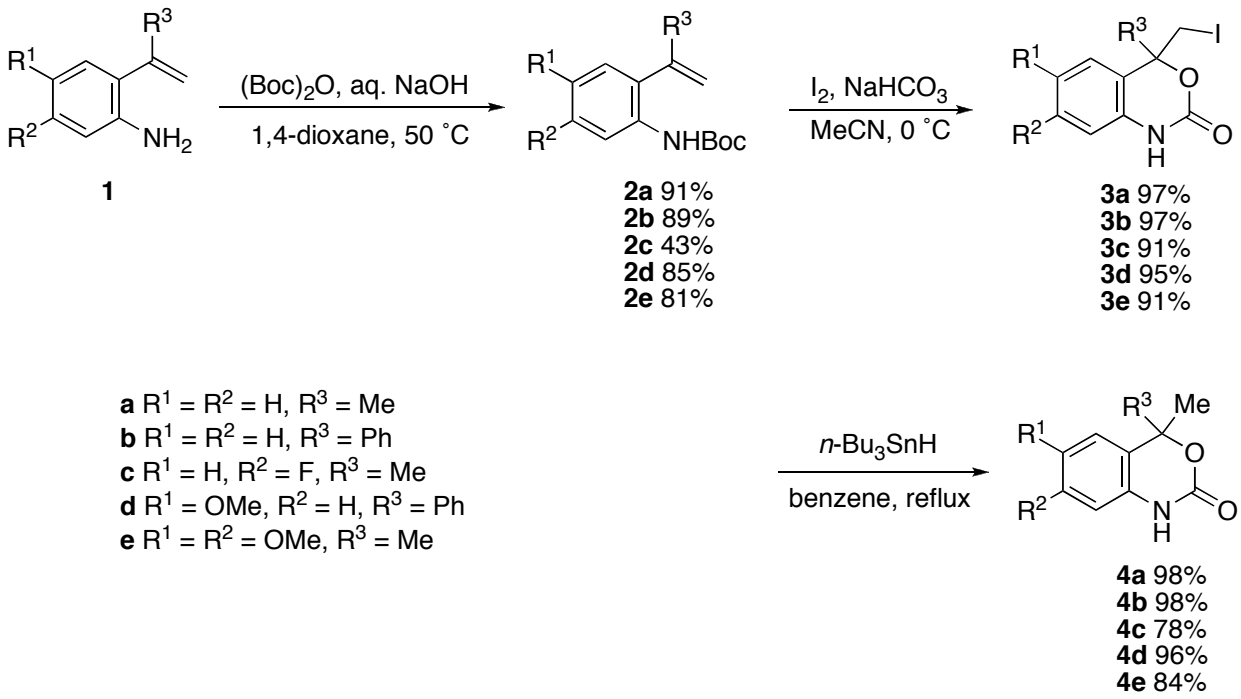
Department of Materials Science, Faculty of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan

Abstract - It has been found that *t*-butyl 2-vinylphenylcarbamate derivatives underwent iodocyclization on treatment with iodine in the presence of sodium hydrogencarbonate to afford 4-iodomethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives in generally good yields. The reduction of these 4-iodomethyl derivatives with tributyltin hydride gave the corresponding 4-methyl derivatives in good yields.

We previously demonstrated that the preparation of 4*H*-1,3-benzodioxin-2-one derivatives could be achieved by iodocyclization of *t*-butyl 2-vinylphenyl carbonate derivatives, derived from *t*-butoxycarbonylation of 2-vinylphenol derivatives.[1] As an extension of this cyclization reaction, we anticipated that a similar sequence starting with 2-aminostyrene derivatives should lead to formation of 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives. We report here on details concerning the results of our investigation which provide a new and simple method for constructing the 1,4-dihydro-2*H*-3,1-benzoxazin-2-one skeleton.[2] Compounds having this skeleton have attracted considerable attention of medicinal and synthetic organic chemists, because some of them have been reported to exhibit a variety of biological activities,[3] such as HIV-1 reverse transcriptase inhibitory[3a] and progesterone receptor antagonistic activities.[3b,e] 1-Substituted 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives have been used as precursors for the generation of the corresponding aza-*o*-quinodimethane intermediates.[4] Most of the previous syntheses of 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives have been based on the reaction of 2-aminobenzyl alcohol derivatives with phosgene,[3,5,6] though Nishiyama, Naitoh, and Sonoda have recently reported a synthesis of 4-nonsubstituted derivatives by selenium-catalyzed carbonylation of 2-nitrobenzyl alcohols.[7]

We conducted reactions of *t*-butyl 2-vinylphenylcarbamates (**2**), which were easily prepared by *t*-butoxycarbonylation of 2-aminostyrene derivatives (**1**) with di-*t*-butyl dicarbonate under the conditions

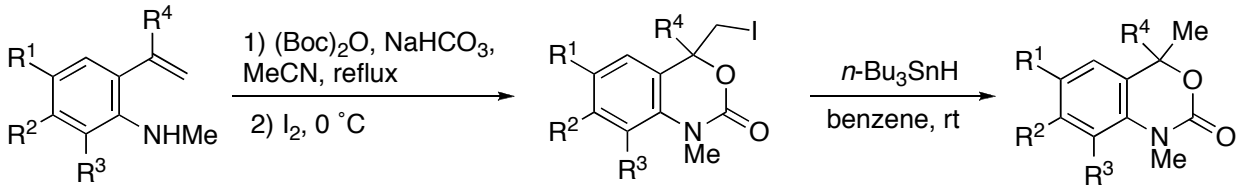
reported by Misawa et al,[8] with iodine in the presence of sodium hydrogencarbonate in acetonitrile at 0 ˚C, as outlined in Scheme 1. The iodocyclization reaction proceeded very smoothly (within 5 min) to afford the expected 4-iodomethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives (**3**) in excellent yields. Attempts to obtain the products (**3**) in one-pot were unsuccessful. Addition of iodine to the reaction mixtures of **1** and di-*t*-butyl dicarbonate resulted in the formation of intractable mixtures of products, from which only very low yields of the desired products were isolated. In order to displace the iodine of **3** with hydrogen, compounds (**3**) were allowed to react with tributyltin hydride in benzene. Although the reaction needed heating at reflux temperature for the times given in Experimental section due to low solubility of **3** in the solvent, the corresponding 4-methyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives (**4**) were obtained in good to excellent yields. These results are also summarized in Scheme 1.



Scheme 1

We found that preparation of 1-methyl-4-iodomethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives (**6**) could be carried out in one-pot from 2-(*N*-methylamino)styrene derivatives (**5**), as illustrated in Scheme 2. Thus, compounds (**5**) were treated with di-*t*-butyl dicarbonate in the presence of sodium hydrogencarbonate in acetonitrile at reflux temperature for the times given in Experimental section. After cooling to 0 ˚C, iodine was added to the resulting reaction mixtures. The iodocyclization reactions went to completion within 30 min to afford the desired products (**6**). The *t*-butoxycarbonylation of less reactive starting materials (**5d**) and (**5e**) proceeded much more sluggishly than **5a-c** and required considerably prolonged reaction times. As the result of the low reactivity in the *t*-butoxycarbonylation

step, rather decreased yields of the desired 4-iodomethyl derivatives (**6d**) and (**6e**), respectively, were obtained after iodocylization. The reduction of 4-iodomethyl derivatives (**6**) using tributyltin hydride proceeded very smoothly even at room temperature to afford the corresponding 4-methyl derivatives (**7**) in fair to good yields. These results are also shown in Scheme 2. Attempts at one-pot production of **3** from **1** under conditions similar to those for the preparation of **6** were all in vain, because *t*-butoxycarbonylation of **1** proceeded very sluggishly.



a $R^1 = R^2 = R^3 = H$, $R^4 = Me$
b $R^1 = R^2 = R^3 = H$, $R^4 = Ph$
c $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = Me$
d $R^1 = R^3 = H$, $R^2 = Cl$, $R^4 = Me$
e $R^1 = H$, $R^2 = H$, $R^3 = R^4 = Me$

Scheme 2

In conclusion, a convenient route for the preparation of 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives has been developed. The method may have some potential utility for heterocycle synthesis because of its simplicity and the ready availability of the starting materials.

EXPERIMENTAL

The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. The ^1H NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. Low-resolution mass spectra (EI) were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use.

Starting Materials. Ethyl 2-amino-4-fluorobenzoate,[9] 2-(1-phenylethenyl)benzenamine (**1b**),[10] 4-methoxy-2-(1-phenylethenyl)benzenamine (**1d**),[11] 4,5-dimethoxy-2-(1-methylethenyl)benzenamine (**1e**),[12] *N*-methyl-2-(1-methylethenyl)benzenamine (**5a**),[13] *N*-methyl-2-(1-phenylethenyl)benzenamine (**5b**),[11] 5-chloro-2-(1-methylethenyl)benzenamine,[12] and ethyl 2-amino-3-methylbenzoate[14] were

prepared by the appropriate reported methods. All other chemicals used in this study were commercially available.

2-(2-Amino-4-fluorophenyl)propan-2-ol. This compound was prepared by the reaction of ethyl 2-amino-4-fluorobenzoate[9] with excess MeMgBr in 84% yield; a yellow liquid; R_f 0.53 (THF–hexane, 1:3); IR (neat) 3460, 3367, 1622 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.65 (s, 6H), 1.73 (s, 1H), 4.82 (br s, 2H), 6.32–6.36 (m, 2H), 7.04 (ddd, *J* = 8.2, 6.4, 1.4 Hz, 1H). Anal. Calcd for $C_9H_{12}FNO$: C, 63.89; H, 7.15; N, 8.28. Found: C, 63.65; H, 7.23, N, 8.25.

5-Fluoro-2-(1-methylethenyl)benzenamine (1c). This compound was prepared by thermal dehydration (neat, 10 min at 130 °C) of 2-(2-amino-4-fluorophenyl)propan-2-ol in 75% yield; a yellow liquid; R_f 0.50 (THF–hexane, 1:5); IR (neat) 3479, 3387, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (d, *J* = 0.9 Hz, 3H), 3.93 (br s, 2H), 5.03 (quint, *J* = 0.9 Hz, 1H), 5.29 (quint, *J* = 0.9 Hz, 1H), 6.38–6.44 (m, 2H), 6.96 (dd, *J* = 8.2, 6.2 Hz, 1H). Anal. Calcd for $C_9H_{10}FN$: C, 71.50; H, 6.67; N, 9.26. Found: C, 71.48; H, 6.74; N, 9.37.

***t*-Butyl *N*-[2-(1-Methylethenyl)phenyl]carbamate (2a).**[15] 2-(1-Methylethenyl)benzenamine (0.27 g, 2.0 mmol) was treated with di-*t*-butyl dicarbonate (0.96 g, 4.4 mmol) in 20% aqueous NaOH–1,4-dioxane (3 mL each) at 50 °C[10] for 2 h to give **2a** (0.42 g, 91%); a colorless oil; R_f 0.70 (THF–hexane, 1:3); IR (neat): 3422, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 9H), 2.06 (d, *J* = 1.4 Hz, 3H), 5.01 (q, *J* = 0.9 Hz, 1H), 5.36 (td, *J* = 1.4, 0.9 Hz, 1H), 6.82 (br s, 1H), 7.00 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.10 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.23 (td, *J* = 7.3, 1.4 Hz, 1H), 8.04 (br d, *J* = 7.8 Hz, 1H).

***t*-Butyl *N*-[2-(1-Phenylethenyl)phenyl]carbamate (2b).** This compound was prepared by *t*-butoxycarbonylation of **1b**[10] as described for the preparation of **2a** (reaction time: 8 h); a pale-yellow oil; R_f 0.52 (THF–hexane, 1:10); IR (neat) 3423, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H), 5.34 (d, *J* = 1.4 Hz, 1H), 5.90 (d, *J* = 1.4 Hz, 1H), 6.44 (br s, 1H), 7.06 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.30–7.36 (m, 6H), 8.01 (br d, *J* = 8.2 Hz, 1H). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 76.99; H, 7.28, N, 4.88.

***t*-Butyl *N*-[5-Fluoro-2-(1-methylethenyl)phenyl]carbamate (2c).** This compound was prepared by *t*-butoxycarbonylation of **1c** as described for the preparation of **2a** (reaction time: 3 d): a pale-yellow oil; R_f 0.63 (THF–hexane, 1:10); IR (neat): 3418, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (s, 9H), 2.04 (s, 3H), 5.00 (s, 1H), 5.39 (s, 1H), 6.69 (td, *J* = 8.7, 2.7 Hz, 1H), 6.91 (br s, 1H), 7.03 (dd, *J* = 8.7, 6.4 Hz, 1H), 7.91 (br d, *J* = 11.0 Hz, 1H). Anal. Calcd for $C_{14}H_{18}FNO_2$: C, 66.91; H, 7.22; N, 5.57. Found: C, 66.90; H, 7.28, N, 5.53.

***t*-Butyl *N*-[4-Methoxy-2-(1-phenylethenyl)phenyl]carbamate (2d).** This compound was prepared by *t*-butoxycarbonylation of **1d**[11] as described for the preparation of **2a** (reaction time: 1.5 h); a yellow oil; R_f 0.69 (THF–pentane, 1:4); IR (neat) 3427, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 9H), 3.79 (s, 3H), 5.33 (d, *J* = 1.4 Hz, 1H), 5.87 (d, *J* = 1.4 Hz, 1H), 6.15 (br s, 1H), 6.76 (d, *J* = 3.2 Hz, 1H), 6.90 (dd, *J* =

8.7, 3.2 Hz, 1H), 7.29–7.32 (m, 5H), 7.80 (br s, 1H). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.79; H, 6.98, N, 4.68.

***t*-Butyl *N*-[4,5-Dimethoxy-2-(1-methylethenyl)phenyl]carbamate (2e).** This compound was prepared by *t*-butoxycarbonylation of **1e**[12] as described for the preparation of **2a** (reaction time: 14 h); a white solid; mp 82–84 °C (hexane–THF); IR (KBr) 3354, 1699, 1607 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9H), 2.05 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 4.99 (d, *J* = 0.9 Hz, 1H), 5.34 (d, *J* = 0.9 Hz, 1H), 6.62 (s, 1H), 6.70 (br s, 1H), 7.70 (br, 1H). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.48; H, 7.94, N, 4.76.

Typical Procedure for the Preparation of 3. 4-Iodomethyl-4-methyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (3a). To a stirred mixture of **2a** (0.24 g, 1.0 mmol) and $NaHCO_3$ (0.26 g, 3.1 mmol) in MeCN (3 mL) at 0 °C was added iodine (0.78 g, 3.1 mmol) by portions. After 5 min, 10% aqueous $Na_2S_2O_3$ was added until the color of iodine disappeared, and the organic materials were extracted with Et_2O three times (10 mL each). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residual solid was recrystallized from hexane–THF to give **3a** (0.29 g, 97%): a white solid; mp 193 °C (decomp) (hexane–THF); IR (KBr) 3215, 1705 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.73 (s, 3H), 3.70 (d, *J* = 11.0 Hz, 1H), 3.85 (d, *J* = 11.0 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 7.01 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.24 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 10.25 (s, 1H); MS *m*/*z* 303 (M^+, 25), 162 (100). Anal. Calcd for $C_{10}H_{10}INO_2$: C, 39.63; H, 3.33; N, 4.62. Found: C, 39.52; H, 3.32; N, 4.60.

4-Iodomethyl-4-phenyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (3b): a pale-yellow solid; mp 177–179 °C (hexane–THF); IR (KBr): 3208, 1709 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.02 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 7.16 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.29–7.38 (m, 6H), 7.59 (d, *J* = 7.8 Hz, 1H), 10.34 (br s, 1H); MS *m*/*z* 365 (M^+, 15), 224 (100). Anal. Calcd for $C_{15}H_{12}INO_2$: C, 49.34; H, 3.31; N, 3.84. Found: C, 49.38; H, 3.29; N, 3.80.

7-Fluoro-4-iodomethyl-4-methyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (3c): a white solid; mp 169–171 °C (hexane–CH_2Cl_2).; IR (KBr) 3227, 1713, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.91 (s, 3H), 3.58 (d, *J* = 11.0 Hz, 1H), 3.62 (d, *J* = 11.0 Hz, 1H), 6.61 (dd, *J* = 10.2, 2.3 Hz, 1H), 6.80 (td, *J* = 8.7, 2.3 Hz, 1H), 7.10 (dd, *J* = 8.7, 5.5 Hz, 1H), 8.71 (br s, 1H); MS *m*/*z* 321 (M^+, 14), 180 (100). Anal. Calcd for $C_{10}H_9FINO_2$: C, 37.41; H, 2.83; N, 4.36. Found: C, 37.30; H, 2.80; N, 4.11.

4-Iodomethyl-6-methoxy-4-phenyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (3d): a white solid; mp 150 °C (decomp) (Et_2O–THF); IR (KBr) 3206, 1713 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.77 (s, 3H), 3.99 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.91 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.21 (d, *J* = 2.7 Hz, 1H), 7.29–7.37 (m, 5H), 10.13 (br s, 1H); MS *m*/*z* 395 (M^+, 31), 224 (100). Anal. Calcd for $C_{16}H_{14}INO_2$: C, 48.63; H, 3.57; N, 3.54. Found: C, 48.41; H, 3.73; N, 3.42.

4-Iodomethyl-6,7-dimethoxy-4-methyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (3e): a white solid; mp

143 °C (decomp) (hexane–THF); IR (KBr) 3223, 1717, 1627, 1612 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.63 (s, 3H), 3.60 (d, J = 11.5 Hz, 1H), 3.62 (s, 6H), 3.76 (d, J = 11.5 Hz, 1H), 6.37 (s, 1H), 6.79 (s, 1H), 9.89 (br s, 1H); MS m/z 363 (M^+, 45), 222 (100). Anal. Calcd for $C_{12}H_{14}INO_2$: C, 39.69; H, 3.89; N, 3.86. Found: C, 39.32; H, 3.87; N, 3.85.

Typical Procedure for the Reduction of 3 to 4. 4,4-Dimethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (4a). A solution of **3a** (0.12 g, 0.40 mmol) in benzene (3 mL) containing *n*-Bu_3SnH (0.22 g, 0.80 mmol) was heated at reflux temperature for 2 h. After evaporation of the solvent, the precipitate was collected by filtration and recrystallization from hexane–Et_2O to give **4a** (69 mg, 98%); a pale-yellow solid; mp 111–113 °C (lit.,[4] 115–116 °C); IR (KBr) 3231, 1711, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (s, 6H), 6.82 (d, J = 7.8 Hz, 1H), 7.06 (ddd, J = 7.8, 7.3, 0.9 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.24 (ddd, J = 7.8, 7.3, 1.4 Hz, 1H), 8.20 (br s, 1H); MS m/z 177 (M^+, 87), 133 (100).

4-Methyl-4-phenyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (4b): reflux time: 8h; colorless needles; mp 219–221 °C (THF); IR (KBr) 3206, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (s, 3H), 6.80 (d, J = 7.8 Hz, 1H), 7.03 (dd, J = 7.8, 7.3 Hz, 1H), 7.13 (d, J = 7.3 Hz, 2H), 7.18–7.26 (m, 4H), 7.35 (d, J = 7.3 Hz, 1H), 10.13 (br s, 1H); MS m/z 239 (M^+, 11), 194 (100). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.12; H, 5.37; N, 5.73.

7-Fluoro-4,4-dimethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (4c): reflux time: 1 h; colorless needles; mp 140–142 °C (hexane–Et_2O); IR (KBr) 3300, 1742, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (s, 6H), 6.59 (dd, J = 9.2, 2.3 Hz, 1H), 6.76 (td, J = 8.7, 2.3 Hz, 1H), 7.10 (dd, J = 8.7, 5.5 Hz, 1H), 8.72 (br s, 1H); MS m/z 195 (M^+, 53,), 180 (100). Anal. Calcd for $C_{10}H_{10}FNO_2$: C, 61.53; H, 5.16; N, 7.18. Found: C, 61.13; H, 5.23; N, 7.07.

6-Methoxy-4-methyl-4-phenyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (4d): reflux time: 24 h; a colorless needles; mp 164–166 °C (hexane–$CHCl_3$); IR (KBr) 3204, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, 3H), 3.82 (s, 3H), 6.75 (d, J = 7.3 Hz, 1H), 6.84–6.87 (m, 2H), 7.26–7.30 (m, 5H), 7.79 (br s, 1H); MS m/z 269 (M^+, 44), 224 (100). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.03; H, 5.70; N, 5.10.

6,7-Dimethoxy-4,4-dimethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (4e): reflux time: 36 h; pale-yellow needles; mp 136–138 °C (hexane–CH_2Cl_2); IR (KBr) 3265, 1705, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (s, 6H), 3.865 (s, 3H), 3.867 (s, 3H), 6.39 (s, 1H), 6.63 (s, 1H), 8.88 (br s, 1H); MS m/z 237 (M^+, 100). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.57; H, 6.37; N, 5.84.

***N*-[4,5-Dimethoxy-2-(1-methylethenyl)phenyl]formamide.** This compound was prepared by treating 4,5-dimethoxy-2-(1-methylethenyl)benzenamine[12] with formic acid in toluene at reflux temperature under azeotropic conditions in 78 yield; a light-brown oil; R_f 0.39 (AcOEt–hexane, 1:1); IR (neat) 3320, 1682, 1611 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.03 and 2.06 (2s, combined 3H), 3.86, 3.88, 3.90, and 3.91 (4s,

combined 6H), 4.98 and 5.02 (2s, combined 1H), 5.32 and 5.39 (2s, combined 1H), 6.65 (s, 1H), 6.69 and 6.71 (2s, combined 1H), 7.36–8.54 (m, 2H). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.59; H, 6.84; N, 6.23.

***N*-Methyl-4,5-dimethoxy-2-(1-methylethenyl)benzenamine (5c).** This compound was prepared by the LAH reduction of the above formamide in Et_2O at room temperature in 79% yield; a light-brown oil; R_f 0.26 (THF–hexane, 1:7); IR (neat) 3416, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H), 2.83 (s, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 3.96 (br, 1H), 5.01 (s, 1H), 5.27 (s, 1H), 6.28 (s, 1H), 6.65 (s, 1H). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.48; H, 8.60; N, 6.78.

***N*-[5-Chloro-2-(1-methylethenyl)]phenylformamide.** This compound was prepared by treating 5-chloro-2-(1-methylethenyl)benzenamine[12] with formic acid in toluene at reflux temperature under azeotropic conditions in 77% yield; a pale-yellow oil; R_f 0.31 (AcOEt–hexane, 1:3); IR (neat) 3312, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 and 2.06 (s and d, J = 1.4 Hz, combined 3H), 5.00 and 5.04 (2s, combined 1H), 5.43 and 5.44 (s, and d, J = 1.4 Hz, combined 1H), 7.08–7.22 (m, 3H), 7.58–8.71 (m, 2H). Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.08; H, 4.96; N, 7.56.

5-Chloro-*N*-methyl-2-(1-methylethenyl)benzenamine (5d). This compound was prepared by the LAH reduction of *N*-[5-chloro-2-(1-methylethenyl)]phenylformamide in Et_2O at room temperature in 64% yield; a pale-yellow liquid; R_f 0.42 (benzene–hexane, 1:10); IR (neat) 3429, 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (t, J = 1.4 Hz, 3H), 2.81 (d, J = 4.6 Hz, 3H), 4.24 (br s, 1H), 5.00 (q, J = 1.4 Hz, 1H), 5.29 (q, J = 1.4 Hz, 1H), 6.56 (d, J = 2.3 Hz, 1H), 6.63 (dd, J = 7.8, 2.3 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H). Anal. Calcd for $C_{10}H_{12}ClN$: C, 66.12; H, 6.66; N, 7.71. Found: C, 65.92; H, 6.68; N, 7.71.

2-(2-Amino-3-methylphenyl)propan-2-ol. This compound was prepared by the reaction of ethyl 2-amino-3-methylbenzoate[6] with excess MeMgBr in Et_2O at 0 °C in 83% yield; a pale-yellow needle; mp 66–68 °C (hexane); IR (KBr) 3385, 3254 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (s, 7H), 2.18 (s, 3H), 4.50 (br s, 2H), 6.62 (dd, J = 7.8, 7.3 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.49; H, 9.19; N, 8.48.

2-Methyl-6-(1-methylethenyl)benzenamine.[16] This compound was prepared by thermal dehydration (neat, 2h at 220 °C) of 2-(2-amino-3-methylphenyl)propan-2-ol in 59% yield; a pale-yellow liquid; R_f 0.33 (Et_2O–hexane, 1:10); IR (neat) 3474, 3383, 1614 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (dd, J = 1.4, 0.9 Hz. 3H), 2.19 (s, 3H), 3.81 (br s, 2H), 5.05 (q, J = 0.9 Hz, 1H), 5.30 (q, J = 1.4 Hz, 1H), 6.80 (dd, J = 7.8, 7.3 Hz, 1H), 6.92 (dd, J = 7.8, 1.4 Hz, 1H), 6.97 (d, J = 7.3 Hz, 1H).

***N*-[2-Methyl-6-(1-methylethenyl)]phenylformamide.** This compound was prepared by treating 2-methyl-6-(1-methylethenyl)benzeneamine[7] with formic acid in toluene at reflux temperature under azeotropic conditions in 49% yield; white needle; mp 80–83 °C (hexane–CH_2Cl_2); IR (KBr) 3202, 1674, 1661, 1636 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (d, J = 0.9 Hz, 3H), 2.29 and 2.33 (2s, combined 3H), 4.91 and 4.50 (2q, J = 0.9 Hz each, combined 1H), 5.20 and 5.26 (2q, J = 0.9 Hz each, combined 1H),

6.92–7.20 (m, 4H), 8.17–8.35 (m, 1H). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.46; H, 7.54; N, 7.89.

2,*N*-Dimethyl-6-(1-methylethenyl)benzenamine (5e). This compound was prepared by the LAH reduction of *N*-[2-methyl-6-(1-methylethenyl)]phenylformamide in Et_2O at room temperature in 63% yield; a pale-yellow liquid; R_f 0.53 (THF–hexane, 1:7); IR (neat) 3377, 1634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (d, *J* = 1.4 Hz, 3H), 2.31 (s, 3H), 2.78 (s, 3H), 3.56 (br, 1H), 4.97 (d, *J* = 0.9 Hz, 1H), 5.22 (q, *J* = 1.4 Hz, 1H), 6.82 (dd, *J* = 7.8, 7.3 Hz, 1H), 6.93 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.04 (dd, *J* = 7.3, 0.9 Hz, 1H). Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.81; H, 9.30; N, 8.52.

Typical Procedure for the preparation of 6. 4-Iodomethyl-1,4-dimethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (6a). A mixture of **5a** (0.30 g, 2.0 mmol), $(Boc)_2O$ (1.1 g, 5.0 mmol), and $NaHCO_3$ (1.3 g, 15 mmol) in MeCN (10 mL) was heated at reflux temperature for 2.5 h. The mixture was cooled to 0 °C and iodine (1.5 g, 6.0 mmol) was added. After stirring for 30 min, 10% aqueous $Na_2S_2O_3$ was added until the color of iodine disappeared. The precipitate was collected by filtration and recrystallized from hexane–CH_2Cl_2 gave **6a** (0.52 g, 84%); a white solid; mp 133 °C (hexane–CH_2Cl_2); IR (KBr) 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (s, 3H), 3.41 (s, 3H), 3.56 (d, *J* = 11.0 Hz, 1H), 3.60 (d, *J* = 11.0 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 7.14 (ddd, *J* = 7.8, 7.3, 0.9 Hz, 1H), 7.18 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.38 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H); MS *m*/*z* 317 (M^+, 9.7), 176 (100). Anal. Calcd for $C_{11}H_{12}INO_2$: C, 41.66; H, 3.81; N, 4.42. Found: C, 41.58; H, 3.85; N, 4.15.

4-Iodomethyl-1-methyl-4-phenyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (6b): pale-yellow needles; mp 185 °C (decomp) (hexane–CH_2Cl_2); IR (KBr) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26 (s, 3H), 3.86 (d, *J* = 11.4 Hz, 1H), 3.89 (d, *J* = 11.4 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 7.25 (td, *J* = 7.3, 0.9 Hz, 1H), 7.32 (s, 5H), 7.36 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.44 (ddd, *J* = 8.2, 7.3, 1.4 Hz, 1H); MS *m*/*z* 379 (M^+, 15), 238 (100). Anal. Calcd for $C_{16}H_{14}INO_2$: C, 50.68; H, 3.72; N, 3.69. Found: C, 50.63; H, 3.62; N, 3.59.

4-Iodomethyl-6,7-dimethoxy-1,4-dimethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (6c): a pale-yellow solid; mp 110–112 °C (hexane–Et_2O); IR (KBr): 1712, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (s, 3H), 3.40 (s, 3H), 3.53 (d, *J* = 11.0 Hz, 1H), 3.57 (d, *J* = 11.0 Hz, 1H), 3.89 (s, 3H), 3.93 (s, 3H), 6.49 (s, 1H), 6.67 (s, 1H). MS *m*/z 377 (M^+, 16), 236 (100). Anal. Calcd for $C_{13}H_{16}INO_4$: C, 41.40; H, 4.28; N, 3.71. Found: C, 41.30; H, 4.19; N, 3.41.

7-Chloro-4-iodomethyl-1,4-dimethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (6d): reaction time of **5d** with $(Boc)_2O$: 2 days; a pale-yellow solid; mp 103–105 °C (hexane–Et_2O); IR (KBr) 1715, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (s, 3H), 3.39 (s, 3H), 3.55 (d, *J* = 11.0 Hz, 1H), 3.56 (d, *J* = 11.0 Hz, 1H), 6.95 (d, *J* = 1.8 Hz, 1H), 7.08–7.13 (m, 2H). MS *m*/z 351 (M^+, 16), 210 (100). Anal. Calcd for $C_{11}H_{11}ClINO_2$: C, 37.58; H, 3.15; N, 3.98. Found: C, 37.21; H, 3.15; N, 3.92.

4-Iodomethyl-1,4,8-trimethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (6e): reaction time of **5e** with $(Boc)_2O$: 1 day; pale-yellow solid; mp 100–102 °C (hexane–CH_2Cl_2); IR (KBr): 1710 cm^{-1}; ^1H NMR

($CDCl_3$) δ 1.83 (s, 3H), 2.43 (s, 3H), 3.47 (s, 3H), 3.53 (d, *J* = 11.0 Hz, 1H), 3.57 (d, *J* = 11.0 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 7.07 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H); MS *m/z* 331 (M^+, 39), 190 (100). Anal. Calcd for $C_{12}H_{14}INO_2$: C, 43.52; H, 4.26; N, 4.23. Found: C, 43.38; H, 4.56; N, 4.18.

Typical Procedure for the Reduction of 6 to 7. 1,4,4-Trimethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (7a).[5] A solution of **6a** (0.13 g, 0.41 mmol) and *n*-Bu_3SnH (0.23 g, 0.83 mmol) in benzene (3 mL) was stirred overnight at rt. After evaporation of the solvent, the precipitate was collected by filtration and recrystallized from hexane–CH_2Cl_2 to give **7a** (0.13 g, 71%); white solid; mp 92 °C; IR (KBr) 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (s, 6H), 3.41 (s, 3H), 6.95 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.18 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.33 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H); MS *m/z* (%) 191 (M^+, 25), 176 (25), 132 (100).

1,4-Dimethyl-4-phenyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (7b): a pale-yellow solid; mp 80–81 °C (hexane–Et_2O); IR (KBr) 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H), 3.25 (s, 3H), 6.95 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.27–7.31 (m, 5H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.40 (dd, *J* = 7.8, 7.3 Hz, 1H). MS *m/z* 253 (M^+, 11), 208 (56), 194 (100). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.65; H, 6.05; N, 5.46.

6,7-Dimethoxy-1,4,4-trimethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (7c): a pale-yellow solid; mp 104–106 °C (hexane–Et_2O); IR (KBr) 1699, 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (s, 6H), 3.40 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 6.49 (s, 1H), 6.67 (s, 1H); MS *m/z* 252 (M^+, 53), 236 (57), 192 (100). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.13; H, 6.80; N, 5.36.

7-Chloro-1,4,4-trimethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (7d): a pale-yellow solid; mp 64–67 °C (hexane–Et_2O); IR (KBr) 1715, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67 (s, 6H), 3.39 (s, 3H), 6.93 (d, *J* = 1.8 Hz, 1H), 7.07 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H); MS *m/z* 225 (M^+, 43,), 210 (64), 166 (100). Anal. Calcd for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.53; H, 5.37; N, 6.17.

1,4,4,8-Tetramethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one (7e): a pale-yellow solid; mp 99–102 °C (hexane–Et_2O); IR (KBr) 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (s, 6H), 2.42 (s, 3H), 3.47 (s, 3H), 7.02 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.04 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.13 (dd, *J* = 7.8, 1.4 Hz, 1H); MS *m/z* 205 (M^+, 22), 190 (58), 146 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.17; H, 7.53; N, 6.78.

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