CONVENIENT SYNTHESIS OF 1,4-DIHYDRO-2H-3,1-BENZOXAZIN-2-ONES BY IODOCYCLIZATION OF \textit{t}-BUTYL 2-VINYLPHENYLCARBAMATES

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Abstract - It has been found that \textit{t}-butyl 2-vinylphenylcarbamate derivatives underwent iodocyclization on treatment with iodine in the presence of sodium hydrogen carbonate to afford 4-iodomethyl-1,4-dihydro-2H-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\textit{H}-1,3-benzodioxin-2-one derivatives could be achieved by iodocyclization of \textit{t}-butyl 2-vinylphenyl carbonate derivatives, derived from \textit{t}-butoxycarbonylation of 2-vinylphenol derivatives.\textsuperscript{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\textit{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\textit{H}-3,1-benzoxazin-2-one skeleton.\textsuperscript{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,\textsuperscript{3} such as HIV-1 reverse transcriptase inhibitory\textsuperscript{3a} and progesterone receptor antagonistic activities.\textsuperscript{3b, e} 1-Substituted 1,4-dihydro-2\textit{H}-3,1-benzoxazin-2-one derivatives have been used as precursors for the generation of the corresponding aza-\textit{a}-quinodimethane intermediates.\textsuperscript{4} Most of the previous syntheses of 1,4-dihydro-2\textit{H}-3,1-benzoxazin-2-one derivatives have been based on the reaction of 2-aminobenzyl alcohol derivatives with phosgene,\textsuperscript{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.\textsuperscript{7}

We conducted reactions of \textit{t}-butyl 2-vinylphenylcarbamates (2), which were easily prepared by \textit{t}-butoxycarbonylation of 2-aminostyrene derivatives (1) with di-\textit{t}-butyl dicarbonate under the conditions
reported by Misawa et al.\(^8\) with iodine in the presence of sodium hydrogen carbonate 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-2H-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-2H-3,1-benzoxazin-2-one derivatives (4) were obtained in good to excellent yields. These results are also summarized in Scheme 1.

![Scheme 1](image)

We found that preparation of 1-methyl-4-iodomethyl-1,4-dihydro-2H-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 hydrogen carbonate 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 iodocyclization. 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.

![Scheme 2](image)

In conclusion, a convenient route for the preparation of 1,4-dihydro-2H-3,1-benoxazin-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 $^1$H 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-fluorobenzoate9 with excess MeMgBr in 84% yield; a yellow liquid; Rf 0.53 (THF–hexane, 1:3); IR (neat) 3460, 3367, 1622 cm⁻¹; ¹H NMR (CDCl₃): 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 C₁₀H₁₂FNO: 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; Rf 0.50 (THF–hexane, 1:5); IR (neat) 3479, 3387, 1620 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₀H₁₂FN: 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).** 2-(1-Methylethenyl)benzenamine (0.27 g, 2.0 mmol) was treated with di-t-butyldicarbonate (0.96 g, 4.4 mmol) in 20% aqueous NaOH–1.4-dioxane (3 mL each) at 50 °C for 2 h to give 2a (0.42 g, 91%); a colorless oil; Rf 0.70 (THF–hexane, 1:3); IR (neat): 3422, 1732 cm⁻¹; ¹H NMR (CDCl₃) 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-Phenylenethenyl)phenyl]carbamate (2b).** This compound was prepared by t-butoxycarbonylation of 1b as described for the preparation of 2a (reaction time: 8 h); a pale-yellow oil; Rf 0.52 (THF–hexane, 1:10); IR (neat) 3423, 1732 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₅H₁₄NO₂: 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; Rf 0.63 (THF–hexane, 1:10); IR (neat): 3418, 1732 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₅H₁₄FNO₂: 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 as described for the preparation of 2a (reaction time: 1.5 h); a yellow oil; Rf 0.69 (THF–pentane, 1:4); IR (neat) 3427, 1732 cm⁻¹; ¹H NMR (CDCl₃) 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 = 8.2, 6.4 Hz, 1H), 7.04 (ddd, J = 8.2, 6.2 Hz, 1H). Anal. Calcd for C₁₅H₁₄O₂N: C, 77.26; H, 7.17; N, 4.74. Found: C, 76.99; H, 7.28, N, 4.88.
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\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 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\(_{39}\)H\(_{46}\)N\(_{2}\): C, 73.79; H, 6.98, N, 4.68.

**Typical Procedure for the Preparation of 3. 4-Iodomethyl-4-methyl-1,4-dihydro-2H-3,1-benzoazin-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\(_2\)S\(_2\)O\(_3\) was added until the color of iodine disappeared, and the organic materials were extracted with Et\(_2\)O three times (10 mL each). The combined extracts were washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), 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\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 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\(_{16}\)H\(_{23}\)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-2H-3,1-benzoazin-2-one (3b): a pale-yellow solid; mp 177–179 °C (hexane–THF); IR (KBr): 3208, 1709 cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 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\(_{19}\)H\(_{22}\)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-2H-3,1-benzoazin-2-one (3c): a white solid; mp 169–171 °C (hexane–CH\(_2\)Cl\(_2\)); IR (KBr) 3227, 1713, 1616 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 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\(_{19}\)H\(_{22}\)FNO\(_2\): C, 37.41; H, 2.83; N, 4.46. Found: C, 37.30; H, 2.80; N, 4.11.

4-Iodomethyl-6-methoxy-4-phenyl-1,4-dihydro-2H-3,1-benzoazin-2-one (3d): a white solid; mp 150 °C (decomp) (Et\(_3\)O–THF): IR (KBr) 3206, 1713 cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 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\(_{18}\)H\(_{21}\)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-2H-3,1-benzoazin-2-one (3e): a white solid; mp
143 °C (decomp) (hexane–THF); IR (KBr) 3223, 1717, 1627, 1612 cm⁻¹; ¹H NMR (DMSO-d₆) 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 C₁₁₂H₁₄INO₂: 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-2H-3,1-benzoxazin-2-one (4a). A solution of 3a (0.12 g, 0.40 mmol) in benzene (3 mL) containing n-Bu₃SnH (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–Et₂O to give 4a (69 mg, 98%); a pale-yellow solid; mp 136–143 °C (lit.⁹ 115–116 °C); IR (KBr) 3231, 1728 cm⁻¹; ¹H NMR (CDCl₃) 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-2H-3,1-benzoxazin-2-one (4b): reflux time: 8 h; colorless needles; mp 219–221 °C (THF); IR (KBr) 3206, 1724 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₅H₁₄NO₂: 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-2H-3,1-benzoxazin-2-one (4c): reflux time: 1 h; colorless needles; mp 140–142 °C (hexane–Et₂O); IR (KBr) 3300, 1742, 1616 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₀H₁₀FNO₂: 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-2H-3,1-benzoxazin-2-one (4d): reflux time: 24 h; a colorless needles; mp 164–166 °C (hexane–CHCl₃); IR (KBr) 3204, 1728 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₅H₁₅NO₂: 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-2H-3,1-benzoxazin-2-one (4e): reflux time: 36 h; pale-yellow needles; mp 136–138 °C (hexane–CH₂Cl₂); IR (KBr) 3265, 1705, 1614 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₂H₁₃NO₂: 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)benzenamine¹² with formic acid in toluene at reflux temperature under azeotropic conditions in 78 yield; a light-brown oil; Rf 0.39 (AcOEt–hexane, 1:1); IR ( neat) 3200, 1682, 1611 cm⁻¹; ¹H NMR (CDCl₃): 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: 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-methylene)benzamine (5c). This compound was prepared by the LAH reduction of the above formamide in Et₂O at room temperature in 79% yield; a light-brown oil; Rₐ 0.26 (THF–hexane, 1:7); IR (neat) 3416, 1611 cm⁻¹; ¹H NMR (CDCl₃) 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}NO₂: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.48; H, 8.60; N, 6.78.

N-[5-Chloro-2-(1-methylene)phenyl]formamide. This compound was prepared by treating 5-chloro-2-(1-methylene)benzamine¹² with formic acid in toluene at reflux temperature under azeotropic conditions in 77% yield; a pale-yellow oil; Rₐ 0.31 (AcOEt–hexane, 1:3); IR (neat) 3312, 1682 cm⁻¹; ¹H NMR (CDCl₃) 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-methylene)benzamine (5d). This compound was prepared by the LAH reduction of N-[5-chloro-2-(1-methylene)phenyl]formamide in Et₂O at room temperature in 64% yield; a pale-yellow liquid; Rₐ 0.42 (benzene–hexane, 1:10); IR (neat) 3429, 1636 cm⁻¹; ¹H NMR (CDCl₃) 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_{11}ClNO: 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-methylbenzoate⁶ with excess MeMgBr in Et₂O at 0 °C in 83% yield; a pale-yellow needle; mp 66–68 °C (hexane); IR (KBr) 3385, 3254 cm⁻¹; ¹H NMR (CDCl₃) 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-methylene)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; Rₐ 0.33 (Et₂O–hexane, 1:10); IR (neat) 3474, 3383, 1616 cm⁻¹; ¹H NMR (CDCl₃) 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-methylene)phenyl]formamide. This compound was prepared by treating 2-methyl-6-(1-methylene)benzeneamine⁷ with formic acid in toluene at reflux temperature under azeotropic conditions in 49% yield; white needle; mp 80–83 °C (hexane–CH₂Cl₂); IR (KBr) 3202, 1674, 1661, 1636 cm⁻¹; ¹H NMR (CDCl₃) 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),
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 Et₂O at room temperature in 63% yield; a pale-yellow liquid; Rf 0.53 (THF–hexane, 1:7); IR (neat) 3377, 1634 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₅H₁₃NO: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.46; H, 7.54; N, 7.89.

Typical Procedure for the preparation of 6. 4-Iodomethyl-1,4-dimethyl-1,4-dihydro-2H-3,1-benoxazin-2-one (6a). A mixture of 5a (0.30 g, 2.0 mmol), (Boc)₂O (1.1 g, 5.0 mmol), and NaHCO₃ (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 Na₂S₂O₃ was added until the color of iodine disappeared. The precipitate was collected by filtration and recrystallized from hexane–CH₂Cl₂ gave 6a (0.52 g, 84%); a white solid; mp 133 °C (hexane–CH₂Cl₂); IR (KBr) 1699 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₅H₁₃INO₂: 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-2H-3,1-benoxazin-2-one (6b): pale-yellow needles; mp 185 °C (decomp) (hexane–CH₂Cl₂); IR (KBr) 1715 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₆H₁₃INO₂: 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-2H-3,1-benoxazin-2-one (6c): a pale-yellow solid; mp 110–112 °C (hexane–Et₂O); IR (KBr): 1712, 1616 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₃H₁₄INO₄: 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-2H-3,1-benoxazin-2-one (6d): reaction time of 5d with (Boc)₂O: 2 days; a pale-yellow solid; mp 103–105 °C (hexane–Et₂O); IR (KBr) 1715, 1601 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₁H₁₁ClINO₂: 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-2H-3,1-benoxazin-2-one (6e): reaction time of 5e with (Boc)₂O: 1 day; pale-yellow solid; mp 100–102 °C (hexane–CH₂Cl₂); IR (KBr): 1710 cm⁻¹; ¹H NMR
We wish to acknowledge the helpful assistance of Mrs. Miyuki Tanmatsu of this Department in determining mass spectra and performing combustion analyses.

REFERENCES AND NOTES

Typical Procedure for the Reduction of 6 to 7. 1,4,4-Trimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (7a). A solution of 6a (0.13 g, 0.41 mmol) and n-Bu3SnH (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—Et2O to give 7a (0.13 g, 71%); white solid; mp 92 °C; IR (KBr) 1701 cm⁻¹; ¹H NMR (CDCl₃) 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-2H-3,1-benzoxazin-2-one (7b): a pale-yellow solid; mp 80–81 °C (hexane–Et₂O); IR (KBr) 1711 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₆H₁₄NO₂: 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-2H-3,1-benzoxazin-2-one (7c): a pale-yellow solid; mp 104–106 °C (hexane–Et₂O); IR (KBr) 1699, 1618 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₅H₁₃NO₂: 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-2H-3,1-benzoxazin-2-one (7d): a pale-yellow solid; mp 64–67 °C (hexane–Et₂O); IR (KBr) 1715, 1603 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₅H₁₂ClNO₂: 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-2H-3,1-benzoxazin-2-one (7e): a pale-yellow solid; mp 99–102 °C (hexane–Et₂O); IR (KBr) 1709 cm⁻¹; ¹H NMR (CDCl₃) 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 C₁₂H₁₅NO₂: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.17; H, 7.53; N, 6.78.

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