Synthesis of 4-Alkylidene-4*H*-3,1-benzoxazine Derivatives by Acid-Catalyzed Cyclization of 2-Isocyanophenyl Ketones in the Presence of a Vinyl Ether

Kazuhiro Kobayashi,* Yuta Okamura, Hisatoshi Konishi

Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan
Fax +81(857)315263; E-mail: kkoba@chem.tottori-u.ac.jp

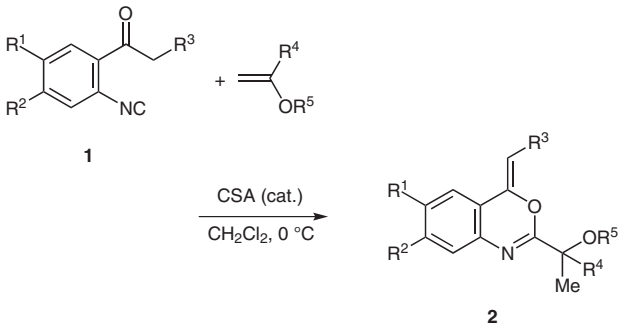
Received 2 December 2008; revised 6 January 2009

Abstract: 2-(1-Alkoxyalkyl)-4-alkylidene-4*H*-3,1-benzoxazines are conveniently prepared by the reaction of 1-(2-isocyanophenyl)ethanones or 1-(2-isocyanophenyl)propan-1-ones with a vinyl ether, such as 2-methoxypropene or ethyl vinyl ether, in the presence of a catalytic amount of (±)-camphor-10-sulfonic acid.

Key words: 4*H*-3,1-benzoxazines, acid-catalyzed reaction, fused-ring system, isocyanides, vinyl ethers

The biological properties of 4-alkylidene-4*H*-3,1-benzoxazines derivatives are of interest because some molecules containing the 4*H*-3,1-benzoxazine skeleton have been reported to exhibit biological activities.[1] Several efficient methods for the preparation of 4*H*-3,1-benzoxazines have been reported,[2] but it is only recently that general syntheses of 4-alkylidene-4*H*-3,1-benzoxazines have been developed. In 2004, Costa et al.[3] reported the synthesis of (3,1-benzoxazin-4-ylidene)acetates by palladium-catalyzed oxidative carbonylation of 2-ethynylaniline derivatives, whereas a synthesis of 1-substituted 3-(4-methylene-4*H*-3,1-benzoxazin-2-yl)phenylureas was reported by Fresneda et al. in 2007.[4] Cacchi et al. reported that 2-substituted 4-arylidene-4*H*-3,1-benzoxazines are formed as byproducts in the synthesis of 2- or 3-arylindoles through palladium- or copper-catalyzed cyclization of 2-ethynylacetoanilides.[5] We report the synthesis of a series of 2-(1-alkoxyalkyl)-4-alkylidene-4*H*-3,1-benzoxazine derivatives **2** by cyclization of 1-(2-isocyanophenyl)ethanones or 1-(2-isocyanophenyl)propan-1-ones **1** with vinyl ethers in the presence of a catalytic amount of an acid.

The 2-isocyanophenyl ketones **1** are easily prepared by N-formylation of the corresponding 2-aminophenyl ketones (which are commercially available or can be prepared by treatment of the corresponding 2-aminobenzonitrile with methyl- or ethylmagnesium bromide, followed by acidic hydrolysis with aqueous HCl) by amidation with formic acid and dehydration of the resulting formamide with phosphoryl chloride in tetrahydrofuran in the presence of triethylamine as a base. The resulting isocyano ketone is treated with a vinyl ether, such as 2-methoxypropene or ethyl vinyl ether, at 0 °C in dichloromethane containing a catalytic amount of (±)-camphor-10-sulfonic acid (CSA) to give the corresponding 2-(1-alkoxyalkyl)-4-alkylidene-4*H*-3,1-benzoxazine **2**, after aqueous workup and purification by crystallization or column chromatography on silica gel, as shown in Scheme 1. Isolated yields of the products **2** are generally good, as summarized in Table 1, although the yields of the products in the reactions using ethyl vinyl ether were somewhat lower than those obtained using 2-methoxypropene. Note that the reaction of 1-(2-isocyano-4,5-dimethoxyphenyl)propan-1-one (**1f**) with 2-methoxypropene gave a rather poor result (entry 10), possibly because of the low reactivity of this isocyanide as a result of the presence of the two methoxy groups.



Scheme 1 Synthesis of 2-(1-alkoxyalkyl)-4-alkylidene-4*H*-3,1-benzoxazine by cyclization of 2-isocyanophenyl ketones

Because isocyanides **1** are rather unstable, they must be freshly prepared for satisfactory production of the desired products **2**. The stereochemistry of the ethylidene moiety of compounds **2c–e** and **2h–j** was shown to be *Z* by means of NOE experiments. For example, a 7.0% enhancement in the signal at δ = 7.35 assignable to the hydrogen at the 5-position in compound **2c** was observed when the signal at δ = 5.24, assignable to the vinyl proton, was irradiated. Unfortunately, reactions of 1-(2-isocyanophenyl)ethanone (**1a**) with cyclic vinyl ethers, such as 2,3-dihydrofuran or 2*H*-3,4-dihydropyran, under the conditions described above resulted in the formation of intractable mixtures of products from which no traces of the corresponding 4-alkylidene-4*H*-3,1-benzoxazines could be isolated.

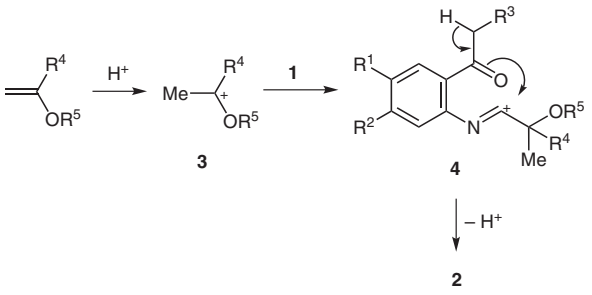
Scheme 2 outlines a probable pathway for the formation of 4-alkylidene-4*H*-3,1-benzoxazines **2** from 2-isocyanophenyl ketones **1** and vinyl ethers. Thus, protonation of a vinyl ether generates a carbocation intermediate **3** that is trapped by the isocyano carbon of **1** to give imidoyl cat-

SYNTHESIS 2009, No. 9, pp 1494–1498
Advanced online publication: 06.03.2009
DOI: 10.1055/s-0028-1087997; Art ID: F24508SS

Table 1 Preparation of 4-Alkylidene-4*H*-1,3-benzoxadines **2**

Entry	2-Isocyanophenyl ketone	Vinyl ether	Product, yield[a] (%)
1	**1a** ($R^1 = R^2 = R^3 = H$)	$R^4 = R^5 = Me$	**2a** 78
2	**1a**	$R^4 = H$; $R^5 = Et$	**2b** 61
3	**1b** ($R^1 = R^2 = H$; $R^3 = Me$)	$R^4 = R^5 = Me$	**2c** 81
4	**1b**	$R^4 = H$; $R^5 = Et$	**2d** 72
5	**1c** ($R^1 = H$; $R^2 = Cl$; $R^3 = Me$)	$R^4 = R^5 = Me$	**2e** 85
6	**1d** ($R^1 = Cl$; $R^2 = R^3 = H$)	$R^4 = R^5 = Me$	**2f** 61
7	**1d**	$R^4 = H$; $R^5 = Et$	**2g** 48
8	**1e** ($R^1 = Cl$; $R^2 = H$; $R^3 = Me$)	$R^4 = R^5 = Me$	**2h** 72
9	**1e**	$R^4 = H$; $R^5 = Et$	**2i** 54
10	**1f** ($R^1 = R^2 = OMe$; $R^3 = Me$)	$R^4 = R^5 = Me$	**2j** 49

[a] Isolated yields.



Scheme 2 Mechanism for the formation of 4-alkylidene-4*H*-3,1-benzoxazines from 2-isocyanophenyl ketones and vinyl ethers

ion intermediate **4**. Attack of the carbonyl oxygen at the cation center of this intermediate, with loss of a proton, then gives rise to benzoxazine **2**.

In conclusion, we have shown that a range of 2-(1-alkoxyalkyl)-4-alkylidene-4*H*-3,1-benzoxazines can be synthesized by the reaction of 2-isocyanophenyl ketones with vinyl ethers in the presence of a catalytic amount of an acid. Although the yields of products are moderate, because of the ready availability of the starting materials and the simplicity of the operations involved, the procedure provides a convenient route to this class of heterocycles, which are difficult to obtain by conventional methods. Further work is in progress to develop synthetic routes to related heterocycles from 2-isocyanophenyl ketones.

All melting points were obtained using a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low- and high-resolution MS spectra (EI, 70 eV) were measured on a JEOL JMS AX505 HA spectrometer. TLC was carried out on Merck Kieselgel 60 PF_{254} plates. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled before use. 1-(2-Isocyanophenyl)ethanone (**1a**) was prepared according to a previously reported procedure.[6] All other chemicals used in this study are commercially available.

2-Aminophenyl Ketones; General Procedure

The following amino ketones were prepared by treating the corresponding 2-aminobenzonitrile with MeMgBr or EtMgBr in Et_2O at r.t., followed by acid hydrolysis with 10% aq HCl.

1-(2-Aminophenyl)propan-1-one

Yield: 66%; pale-yellow solid; mp 44–46 °C (hexane–Et_2O) (Lit.[7] 45–46 °C).

IR (KBr): 3437, 3331, 1645, 1622 cm^{-1}.

^{1}H NMR: δ = 1.21 (t, *J* = 7.3 Hz, 3 H), 2.98 (q, *J* = 7.3 Hz, 2 H), 6.26 (br s, 2 H), 6.64 (t, *J* = 7.3 Hz, 1 H), 6.65 (d, *J* = 7.8 Hz, 1 H), 7.25 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.75 (dd, *J* = 7.3, 0.9 Hz, 1 H).

1-(2-Amino-4-chlorophenyl)propan-1-one

Yield: 52%; yellow solid; mp 74–75 °C (hexane–Et_2O) (Lit.[8] 72–73 °C).

IR (KBr): 3496, 3460, 3366, 3342, 1643, 1609 cm^{-1}.

^{1}H NMR: δ = 1.20 (t, *J* = 7.3 Hz, 3 H), 2.94 (q, *J* = 7.3 Hz, 2 H), 6.36 (br s, 2 H), 6.61 (dd, *J* = 8.7, 2.3 Hz, 1 H), 6.65 (d, *J* = 2.3 Hz, 1 H), 7.67 (d, *J* = 8.7 Hz, 1 H).

1-(2-Amino-5-chlorophenyl)ethanone

Yield: 51%; pale-yellow solid; mp 63–64 °C (hexane–CH_2Cl_2) (Lit.[8] 63–64 °C). The ^{1}H NMR spectral data for this compound were identical to those reported previously.[9]

1-(2-Amino-5-chlorophenyl)propan-1-one

Yield: 67%; yellow solid; mp 79–80 °C (hexane–Et_2O) (Lit.[10] 80–80.5 °C).

IR (KBr): 3497, 3460, 3366, 3342, 1643, 1609 cm^{-1}.

^{1}H NMR: δ = 1.20 (t, *J* = 7.3 Hz, 3 H), 2.94 (q, *J* = 7.3 Hz, 2 H), 6.36 (br s, 2 H), 6.60 (dd, *J* = 8.7, 2.3 Hz, 1 H), 6.65 (d, *J* = 2.3 Hz, 1 H), 7.66 (d, *J* = 8.7 Hz, 1 H).

1-(2-Amino-4,5-dimethoxyphenyl)propan-1-one

Yield: 57%; pale-yellow solid; mp 127–128 °C (hexane–Et_2O) (Lit.[11] 113–114 °C; Lit.[12] 128–129 °C). The spectral (IR and ^{1}H NMR) data were identical to those reported previously.[12]

N-(2-Acylphenyl)formamides

The following formamides were prepared by treatment of the corresponding amino ketones with formic acid in refluxing toluene under azeotropic conditions.

N-(2-Propionylphenyl)formamide[13]

Yield: 85%; pale-yellow needles; mp 37–38 °C (hexane–Et_2O). The spectral data (IR and ^{1}H NMR) for this product were identical to those reported previously.[14]

N-(5-Chloro-2-propionylphenyl)formamide

Yield: 94%; yellow solid; mp 85–86 °C (hexane–Et_2O) (Lit.[8] 86–87 °C).

IR (KBr): 3238, 1692, 1647 cm^{-1}.

^{1}H NMR: δ = 1.22 (t, *J* = 7.3 Hz, 3 H), 3.04 (q, *J* = 7.3 Hz, 2 H), 7.14 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.88 (d, *J* = 8.7 Hz, 1 H), 8.49 (s, 1 H), 8.85 (d, *J* = 1.8 Hz, 1 H), 11.76 (br s, 1 H).

N-(2-Acetyl-4-chlorophenyl)formamide[15]
Yield: 79%; pale-yellow needles; mp 153–154 °C (hexane–CH_2Cl_2).

IR (KBr): 3242, 1701, 1653 cm^{-1}.

^1H NMR: δ = 2.67 (s, 3 H), 7.53 (dd, *J* = 9.1, 2.3 Hz, 1 H), 7.87 (d, *J* = 2.3 Hz, 1 H), 8.49 (s, 1 H), 8.75 (d, *J* = 9.1 Hz, 1 H), 11.50 (br s, 1 H).

N-(4-Chloro-2-propionylphenyl)formamide
Yield: 88%; colorless needles; mp 97–100 °C (hexane–Et_2O).

IR (KBr): 3236, 1692, 1666 cm^{-1}.

^1H NMR: δ = 1.23 (t, *J* = 7.3 Hz, 3 H), 3.06 (q, *J* = 7.3 Hz, 2 H), 7.51 (dd, *J* = 9.2, 2.3 Hz, 1 H), 7.90 (d, *J* = 2.3 Hz, 1 H), 8.48 (s, 1 H), 8.74 (d, *J* = 9.2 Hz, 1 H), 11.55 (br s, 1 H).

Anal. Calcd for $C_{10}H_{10}ClNO_2$; C, 56.75; H, 4.76; N, 6.62. Found: C, 56.62; H, 4.79; N, 6.32.

N-(4,5-Dimethoxy-2-propionylphenyl)formamide[16]
Yield: 84%; pale-yellow solid; mp 130–131 °C (hexane–CH_2Cl_2) (Lit.[17] 125–130 °C).

IR (KBr): 3449, 1683, 1638, 1612 cm^{-1}.

^1H NMR: δ = 1.23 (t, *J* = 7.3 Hz, 3 H), 3.02 (q, *J* = 7.3 Hz, 2 H), 3.91 (s, 3 H), 3.98 (s, 3 H), 7.34 (s, 1 H), 8.46 (d, *J* = 2.3 Hz, 1 H), 8.49 (s, 1 H), 11.95 (br s, 1 H).

2-Isocyanophenyl Ketones 1; General Procedure
The following isocyanides were prepared by the treatment of the corresponding formamides with $POCl_3$–Et_3N in THF at 0 °C.

1-(2-Isocyanophenyl)propan-1-one (1b)
Yield: 87%; yellow oil; R_f = 0.36 (C_6H_6).

IR (neat): 2123, 1699 cm^{-1}.

^1H NMR: δ = 1.25 (t, *J* = 7.3 Hz, 3 H), 3.04 (q, *J* = 7.3 Hz, 2 H), 7.47–7.50 (m, 2 H), 7.53 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.71 (dd, *J* = 7.8, 1.4 Hz, 1 H).

MS: *m/z* (%) = 159 (48) [M^+], 130 (100).

HRMS: *m/z* calcd for $C_{10}H_9NO$: 159.0684; found: 159.0681.

1-(4-Chloro-2-isocyanophenyl)propan-1-one (1c)
Yield: 91%; yellow solid; mp 56–57 °C (hexane–CH_2Cl_2).

IR (KBr): 2131, 1692 cm^{-1}.

^1H NMR: δ = 1.24 (t, *J* = 7.3 Hz, 3 H), 3.03 (q, *J* = 7.3 Hz, 2 H), 7.46–7.48 (m, 2 H), 7.71 (d, *J* = 8.2 Hz, 1 H).

Anal. Calcd for $C_{10}H_8ClNO$; C, 62.03; H, 4.16; N, 7.23. Found: C, 61.83; H, 4.21; N, 7.11.

1-(5-Chloro-2-isocyanophenyl)ethanone (1d)
Yield: 81%; yellow solid; mp 59–60 °C (hexane).

IR (KBr): 2125, 1697, 1653 cm^{-1}.

^1H NMR: δ = 2.72 (s, 3 H), 7.43 (d, *J* = 8.7 Hz, 1 H), 7.52 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.75 (d, *J* = 2.3 Hz, 1 H).

MS: *m/z* (%) = 179 (100) [M^+].

HRMS: *m/z* calcd for C_9H_6ClNO: 179.0138; found: 179.0126.

1-(5-Chloro-2-isocyanophenyl)propan-1-one (1e)
Yield: 70%; yellow oil; R_f = 0.66 (EtOAc–hexane, 1:4).

IR (neat): 2124, 1705 cm^{-1}.

^1H NMR: δ = 1.25 (t, *J* = 7.3 Hz, 3 H), 3.04 (q, *J* = 7.3 Hz, 2 H), 7.42 (d, *J* = 8.2 Hz, 1 H), 7.50 (dd, *J* = 8.2, 2.3 Hz, 1 H), 7.69 (d, *J* = 2.3 Hz, 1 H).

MS: *m/z* (%) = 193 (28) [M^+], 164 (100).

HRMS: *m/z* calcd for $C_{10}H_8ClNO$: 193.0294; found: 193.0315.

1-(2-Isocyano-4,5-dimethoxyphenyl)propan-1-one (1f)
Yield: 63%; pale-yellow solid; mp 104–105 °C (hexane–Et_2O).

IR (KBr): 2112, 1676 cm^{-1}.

^1H NMR: δ = 1.24 (t, *J* = 7.3 Hz, 3 H), 3.11 (q, *J* = 7.3 Hz, 2 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 6.89 (s, 1 H), 7.31 (s, 1 H).

MS: *m/z* (%) = 219 (38) [M^+], 190 (100).

HRMS: *m/z* calcd for $C_{12}H_{13}NO_3$: 219.0895; found: 219.0900.

2-(1-Methoxypropan-2-yl)-4-methylene-4*H*-3,1-benzoxazine (2a); Typical Procedure
To a stirred solution of **1a** (0.33 g, 2.3 mmol) and 2-methoxypropene (0.17 g, 2.3 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added (±)-camphor-10-sulfonic acid (26 mg, 0.11 mmol). After 5 min, sat. aq $NaHCO_3$ (10 mL) was added, and the mixture was extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the residual solid was crystallized from cyclohexane to give **2a** (0.39 g, 78%) as a pale-yellow solid; mp 52–53 °C.

IR (KBr): 1657, 1638, 1603 cm^{-1}.

^1H NMR: δ = 1.52 (s, 6 H), 3.31 (s, 3 H), 4.64 (d, *J* = 2.7 Hz, 1 H), 4.80 (d, *J* = 2.7 Hz, 1 H), 7.21 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.26 (d, *J* = 7.8 Hz, 1 H), 7.33 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.46 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR: δ = 24.41, 51.77, 76.90, 85.78, 120.83, 122.49, 126.57, 127.73, 130.72, 138.12, 151.75, 161.32.

MS: *m/z* (%) = 217 (17) [M^+], 187 (32), 73 (100).

Anal. Calcd for $C_{13}H_{15}NO_2$; C, 71.78; H, 6.96; N, 6.45. Found: C, 71.69; H, 7.08; N, 6.49.

The other products **2b–j** were isolated by column chromatography on silica gel.

2-(1-Ethoxyethyl)-4-methylene-4*H*-3,1-benzoxazine (2b)
Pale-yellow oil; R_f = 0.29 (EtOAc–hexane, 1:6).

IR (neat): 1651, 1628, 1605 cm^{-1}.

^1H NMR: δ = 1.26 (t, *J* = 7.3 Hz, 3 H), 1.50 (d, *J* = 6.9 Hz, 3 H), 3.54 (dq, *J* = 9.2, 7.3 Hz, 1 H), 3.69 (dq, *J* = 9.2, 7.3 Hz, 1 H), 4.09 (q, *J* = 6.9 Hz, 1 H), 4.64 (d, *J* = 1.8 Hz, 1 H), 4.81 (d, *J* = 1.8 Hz, 1 H), 7.21 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.24 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.33 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.46 (dd, *J* = 7.8, 1.4 Hz, 1 H).

MS: *m/z* (%) = 217 (20) [M^+], 174 (100).

Anal. Calcd for $C_{13}H_{15}NO_2$; C, 71.78; H, 6.96; N, 6.45. Found: C, 71.65; H, 7.19; N, 6.34.

(4*Z*)-4-Ethylidene-2-(1-methoxypropan-2-yl)-4*H*-3,1-benzoxazine (2c)
Pale-yellow oil; R_f = 0.42 (THF–hexane, 1:17).

IR (neat): 1672, 1639, 1603 cm^{-1}.

^1H NMR: δ = 1.54 (s, 6 H), 1.78 (d, *J* = 6.9 Hz, 3 H), 3.33 (s, 3 H), 5.24 (q, *J* = 6.9 Hz, 1 H), 7.15 (dd, *J* = 7.8, 7.3 Hz, 1 H), 7.21–7.24 (m, 2 H), 7.33 (d, *J* = 7.8 Hz, 1 H).

MS: *m/z* (%) = 231 (4.8), [M^+], 73 (100).

Anal. Calcd for $C_{14}H_{17}NO_2$; C, 72.70; H, 7.41; N, 6.06. Found: C, 72.69; H, 7.57; N, 5.98.

(4*Z*)-2-(1-Ethoxyethyl)-4-ethylidene-4*H*-3,1-benzoxazine (2d)
Pale-yellow oil; R_f = 0.34 (EtOAc–C_6H_6, 1:20).

IR (neat): 1674, 1643, 1601 cm^{-1}.

^1H NMR: δ = 1.26 (t, *J* = 7.3 Hz, 3 H), 1.51 (d, *J* = 6.9 Hz, 3 H), 1.77 (d, *J* = 7.3 Hz, 3 H), 3.55 (dt, *J* = 9.2, 7.3 Hz, 1 H), 3.71 (dt, *J* = 9.2, 7.3 Hz, 1 H), 4.10 (q, *J* = 7.3 Hz, 1 H), 5.25 (q, *J* = 6.9 Hz, 1 H), 7.15 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.19 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.24 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1 H), 7.33 (dd, *J* = 7.8, 1.4 Hz, 1 H).

MS: *m/z* (%) = 231 (98) [M^+], 73 (100).

Anal. Calcd for $C_{14}H_{17}NO_2$; C, 72.70; H, 7.41; N, 6.06. Found: C, 72.70; H, 7.32; N, 5.91.

(4*Z*)-7-Chloro-4-ethylidene-2-(1-methoxy-1-methylethyl)-4*H*-3,1-benzoxazine (2e)

Colorless crystal; R_f = 0.36 (C_6H_6); mp 54–55 °C (cyclohexane).

IR (KBr): 1672, 1636, 1595 cm^{-1}.

^1H NMR: δ = 1.53 (s, 6 H), 1.77 (d, *J* = 7.3 Hz, 3 H), 3.32 (s, 3 H), 5.23 (q, *J* = 7.3 Hz, 1 H), 7.11 (dd, *J* = 8.2, 2.3 Hz, 1 H), 7.22 (d, *J* = 2.3 Hz, 1 H), 7.24 (d, *J* = 8.2 Hz, 1 H).

MS: *m/z* (%) = 265 (16), [M^+], 73 (100).

Anal. Calcd for $C_{14}H_{16}ClNO_2$; C, 63.28; H, 6.07; N, 5.27. Found: C, 63.25; H, 6.11; N, 5.18.

6-Chloro-2-(1-methoxypropan-2-yl)-4-methylene-4*H*-3,1-benzoxazine (2f)

Pale-yellow crystal; R_f = 0.39 (EtOAc–hexane, 1:10); mp 108–109 °C (hexane).

IR (KBr): 1672, 1638 cm^{-1}.

^1H NMR: δ = 1.51 (s, 6 H), 3.30 (s, 3 H), 4.69 (d, *J* = 3.2 Hz, 1 H), 4.79 (d, *J* = 3.2 Hz, 1 H), 7.19 (d, *J* = 8.2 Hz, 1 H), 7.28 (dd, *J* = 8.2, 2.3 Hz, 1 H), 7.42 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR: δ = 24.34, 51.78, 76.87, 87.12, 122.21, 122.36, 127.96, 130.75, 133.07, 136.74, 150.55, 161.63.

MS: *m/z* (%) = 251 (89) [M^+], 73 (100).

Anal. Calcd for $C_{13}H_{14}ClNO_2$; C, 62.03; H, 5.61; N, 5.56. Found: C, 61.80; H, 5.71; N, 5.52.

6-Chloro-2-(1-ethoxyethyl)-4-methylene-4*H*-3,1-benzoxazine (2g)

Pale-yellow oil; R_f = 0.25 (C_6H_6).

IR (neat): 1660, 1634 cm^{-1}.

^1H NMR: δ = 1.26 (t, *J* = 7.3 Hz, 3 H), 1.49 (d, *J* = 6.9 Hz, 3 H), 3.50–3.56 (m, 1 H), 3.64–3.70 (m, 1 H), 4.08 (q, *J* = 6.9 Hz, 1 H), 4.69 (d, *J* = 3.2 Hz, 1 H), 4.80 (d, *J* = 3.2 Hz, 1 H), 7.17 (d, *J* = 8.7 Hz, 1 H), 7.27 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.42 (d, *J* = 2.3 Hz, 1 H).

MS: *m/z* (%) = 251 (26) [M^+], 207 (67), 73 (100).

Anal. Calcd for $C_{13}H_{14}ClNO_2$; C, 62.03; H, 5.61; N, 5.56. Found: C, 61.95; H, 5.60; N, 5.56.

(4*Z*)-6-Chloro-4-ethylidene-2-(1-methoxypropan-2-yl)-4*H*-3,1-benzoxazine (2h)

Beige oil; R_f = 0.36 (CH_2Cl_2–hexane, 1:2).

IR (neat): 1672, 1639 cm^{-1}.

^1H NMR: δ = 1.53 (s, 6 H), 1.78 (d, *J* = 7.3 Hz, 3 H), 3.32 (s, 3 H), 5.24 (q, *J* = 7.3 Hz, 1 H), 7.14 (d, *J* = 8.2 Hz, 1 H), 7.19 (dd, *J* = 8.2, 2.3 Hz, 1 H), 7.30 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR: δ = 9.65, 24.38, 51.73, 76.93, 98.62, 121.18, 123.40, 127.74, 129.44, 132.88, 136.30, 144.06, 161.66.

MS: *m/z* (%) = 265 (88) [M^+], 73 (100).

Anal. Calcd for $C_{14}H_{16}ClNO_2$; C, 63.28; H, 6.07; N, 5.27. Found: C, 63.13; H, 6.13; N, 5.34.

(4*Z*)-6-Chloro-2-(1-ethoxyethyl)-4-ethylidene-4*H*-3,1-benzoxazine (2i)

Yellow oil; R_f = 0.30 (C_6H_6).

IR (neat): 1672, 1643 cm^{-1}.

^1H NMR: δ = 1.26 (t, *J* = 7.3 Hz, 3 H), 1.50 (d, *J* = 6.9 Hz, 3 H), 1.77 (d, *J* = 7.3 Hz, 3 H), 3.51–3.57 (m, 1 H), 3.66–3.72 (m, 1 H), 4.09 (q, *J* = 6.9 Hz, 1 H), 5.25 (q, *J* = 7.3 Hz, 1 H), 7.12 (d, *J* = 8.7 Hz, 1 H), 7.19 (dd, *J* = 8.7, 2.3 Hz, 1 H), 7.30 (d, *J* = 2.3 Hz, 1 H).

MS: *m/z* (%) = 265 (60) [M^+], 73 (100).

Anal. Calcd for $C_{13}H_{16}ClNO_2$; C, 63.28; H, 6.07; N, 5.27. Found: C, 63.47; H, 5.97; N, 5.46.

(4*Z*)-4-Ethylidene-6,7-dimethoxy-2-(1-methoxypropan-2-yl)-4*H*-3,1-benzoxazine (2j)

Pale-yellow solid; R_f = 0.39 (THF–hexane, 1:7); mp 113–114 °C (hexane–Et_2O).

IR (KBr): 1670, 1638, 1607 cm^{-1}.

^1H NMR: δ = 1.54 (s, 6 H), 1.77 (d, *J* = 6.9 Hz, 3 H), 3.33 (s, 3 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 5.03 (q, *J* = 6.9 Hz, 1 H), 6.76 (s, 1 H), 6.79 (s, 1 H).

MS: *m/z* (%) = 291 (36) [M^+], 73 (100).

Anal. Calcd for $C_{16}H_{21}NO_4$; C, 65.96; H, 7.27; N, 4.81. Found: C, 65.81; H, 7.51; N, 5.01.

Acknowledgment

We are grateful to Mrs. Miyuki Tanmatsu of this university for determining mass spectra and performing combustion analyses.

References

(1) Krantz, A.; Spencer, R. W.; Tam, T. F.; Liak, T. J.; Copp, L. J.; Thomas, E. M.; Refferty, S. P. *J. Med. Chem.* **1990**, *33*, 464.
(2) (a) Lee, H.; Kim, K. *Heteroat. Chem.* **1993**, *4*, 263. (b) El Efrit, M. L.; Hajjem, B.; Zantour, H.; Baccar, B. *Synth. Commun.* **1996**, *26*, 3167. (c) Nishio, T.; Kurokawa, Y.; Narasaki, Y.; Tokunaga, T. *Heterocycles* **2006**, *67*, 247. (d) Gazzaeva, G. A.; Khasanov, M. I.; Mochalov, S. S.; Zefirov, N. S. *Chem. Heterocycl. Comp.* **2007**, *43*, 799. (e) Okuma, K.; Yasuda, T.; Shoji, K.; Yokomori, Y. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1824.
(3) Costa, M.; Della Cà, N.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, *69*, 2469.
(4) Fresneda, P. M.; Bleda, J. A.; Sanz, M. A.; Molina, P. *Synlett* **2007**, 1541.
(5) (a) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363. (b) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843.
(6) Kobayashi, K.; Yoneda, K.; Miyamoto, K.; Morikawa, O.; Konishi, H. *Tetrahedron* **2004**, *60*, 11639.
(7) Lin, S.; Carlson, R. M. *Environ. Sci. Technol.* **1984**, *18*, 743.
(8) Landquist, J. K. *J. Chem. Soc.* **1951**, 1038.
(9) Ames, D. E.; Lovesey, A. C. *J. Chem. Soc.* **1965**, 6036.
(10) Keneford, J. R.; Simpson, J. C. E. *J. Chem. Soc.* **1948**, 354.
(11) Ling, K.-Q.; Sayre, L. M. *Bioorg. Med. Chem.* **2005**, *13*, 3543.
(12) Butin, A. V.; Smirnov, S. K.; Storoganov, T. A.; Bender, W.; Krapivin, G. D. *Tetrahedron* **2007**, *63*, 474.

(13) Nishinaga, A.; Ohara, H.; Tomita, H.; Matsuura, T. *Tetrahedron Lett.* **1983**, *24*, 213.
(14) Simpson, J. C. E.; Atkinson, C. M.; Schofield, K.; Stephenson, O. *J. Chem. Soc.* **1945**, 646.
(15) Niyyoli, T.; Curran, K.; Insaf, S.; McGrandi, M.; Orlowski, M.; Chopra, R.; Agarwal, A.; Howe, A. Y. M.; Prashad, A.; Floyd, M. B.; Johnson, B.; Sutherland, A.; Wheless, K.; Feld, B.; O'Connell, J.; Mansour, T. S.; Bloom, J. *J. Med. Chem.* **2007**, *50*, 2108.
(16) Madding, G. D. *J. Org. Chem.* **1971**, *37*, 1853.
(17) Wohnlich, F. *Arch. Pharm. (Weinheim, Ger.)* **1914**, *251*, 526.