One-Pot Synthesis of 1,4-Dihydro-2-thioxo-2*H*-3,1-benzoxazine-4-acetic Acid Derivatives by the Reaction of 2-Isothiocyanatophenyl Ketones with Lithium Enolates of Acetates and Tertiary Acetamides

by **Kazuhiro Kobayashi***, **Shuhei Fukamachi**, **Akihiro Kobayashi**, and **Aogu Gotoh**

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

The one-pot synthesis of 4-aryl-1,4-dihydro-2-thioxo-2*H*-3,1-benzoxazine-4-acetic acid derivatives **2** was achieved in good yields by the reaction of aryl(2-isothiocyanatophenyl)methanones **1** with lithium enolates of acetates and tertiary acetamides. (2*E*)-1-(2-Isothiocyanatophenyl)-3-phenylprop-2-en-1-one (**3**) gave 1,4-dihydro-4-[(1*E*)-2-phenylethenyl]-2-thioxo-2*H*-3,1-benzoxazine-4-acetic acid derivatives **4** in good yields as well.

Introduction. – The 1,4-dihydro-2*H*-3,1-benzoxazine-2-thione derivatives are important compounds, because some of them exhibit biological activities [1]. A perusal of the literature indicates that this class of heterocycles has been synthesized by the treatment of the respective 1,4-dihydro-2*H*-3,1-benzoxazin-2-one derivatives with *Lawesson* reagent [1a,b,d]. However, this reaction requires rather high temperatures. So, we have recently demonstrated the preparation of 4-substituted and 4,4-disubstituted 1,4-dihydro-2*H*-3,1-benzoxazine-2-thiones by the reaction of 2-lithiophenyl isothiocyanates with aldehydes or ketones [2a], and the preparation of 4-substituted 4-(alkyloxy)-1,4-dihydro-2*H*-3,1-benzoxazine-2-thiones by the reaction of 2-isothiocyanatobenzoates with organolithiums [2b], and we decided to develop a method for the preparation of another type of 1,4-dihydro-2*H*-3,1-benzoxazine-2-thione derivatives by investigating reactions of aryl(2-isothiocyanatophenyl)methanones **1** with organometals. Thus we found that lithium enolates of acetates and tertiary acetamides reacted with **1** cleanly to afford 4-aryl-1,4-dihydro-2-thioxo-2*H*-3,1-benzoxazine-4-acetic acid derivatives **2**. We also found that 1,4-dihydro-4-[(1*E*)-2-phenylethenyl]-2-thioxo-2*H*-3,1-benzoxazine-4-acetic acid derivatives **4** could be obtained similarly from (2*E*)-1-(2-isothiocyanatophenyl)-3-phenylprop-2-en-1-one (**3**). In this article, we report the results of our investigation, which provide a convenient method for the preparation of these new types of 1,4-dihydro-2*H*-3,1-benzoxazine-2-thione derivatives.

Results and Discussion. – The one-pot synthesis of **2** from **1**, readily prepared from (2-aminophenyl)phenylmethanones according to the sequence described previously [3], was conducted as shown in *Scheme 1*. Thus, acetates and tertiary acetamides **1** were treated with lithium diisopropylamide (LDA) in THF at $-78°$ to generate the

corresponding lithium enolates, which were then allowed to react with the 2-isothiocyanatophenyl ketones **1**. The selective attack of the lithium enolates on the C=O C-atom of **1** followed by the addition of the alkoxide moiety of the resulting intermediate **A** to the isothiocyanato C-atom proceeded smoothly. The progress of the reaction was monitored by TLC (SiO_2) for the disappearance of the starting 2-ketone **1**, and the reactions were complete within 10 min. After usual aqueous workup and subsequent purification by column chromatography (silica gel), the desired products **2** were generally obtained in good yields (see *Table*), independently of the substituents at the benzene ring of **1**. Unfortunately, however, when the isothiocyanatophenyl ketones **1** were subjected to reactions with organolithiums such as butyllithium or phenyllithium, considerably complex mixtures of products were formed, from which no more than trace amounts of the desired products were isolated. It should be noted that the use of *Grignard* reagents gave similar results.

Scheme 1

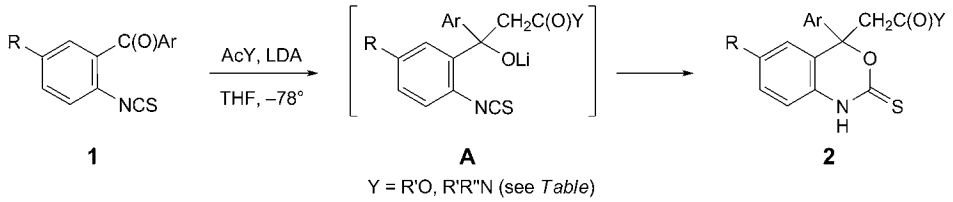


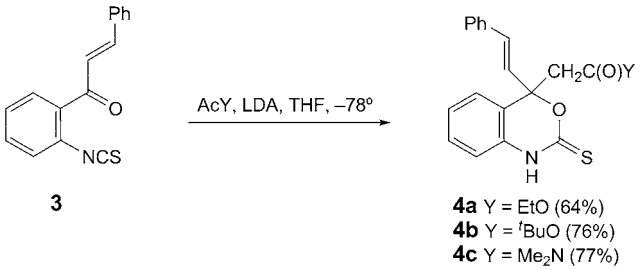
Table. *Preparation of 4-Aryl-2-thioxo-2*H*-1,4-dihydro-3,1-benzoxazine-4-acetic Acid Derivatives* **2**

1	Y	**2**	Yield[a]) [%]
1a (R = H, Ar = Ph)	EtO	**2a**	69
1a	^{t}BuO	**2b**	78
1a	Me_2N	**2c**	78
1a	piperidin-1-yl	**2d**	74
1a	morpholin-4-yl	**2e**	77
1b (R = Cl, Ar = Ph)	EtO	**2f**	78
1b	morpholin-4-yl	**2g**	87
1c (R = H, Ar = 4-Cl–C_6H_4)	^{t}BuO	**2h**	73
1c	Me_2N	**2i**	77
1d (R = H, Ar = 4-MeO–C_6H_4)	^{t}BuO	**2j**	75

[a]) Yields of isolated products.

Subsequently, we were interested in the reactivity of (2*E*)-1-(2-isothiocyanatophenyl)-3-phenylprop-2-en-1-one (**3**) with lithium enolates. We found that when **3** was treated with lithium enolates under the same conditions as described for the preparation of **2**, the addition occurred selectively in the 1,2-addition fashion and not in a 1,4-addition fashion, to afford 1,4-dihydro-4-[(1*E*)-1-phenylethenyl]-2-thioxo-2*H*-3,1-benzoxazine-4-acetic acid derivatives **4** as illustrated in *Scheme 2*. The yields of **4** were comparable to those of **2**.

Scheme 2



3

4a Y = EtO (64%)
4b Y = ^{t}BuO (76%)
4c Y = Me_2N (77%)

In summary, an efficient method for preparing 1,4-dihydro-2*H*-3,1-benzoxazine-2-thione derivatives **2** and **4** by the reaction of aryl(2-isothiocyanatophenyl)methanones **1** and (2*E*)-1-(2-isothiocyanatophenyl)-3-phenylprop-2-en-1-one (**3**), respectively, with lithium enolates of acetates and tertiary acetamides was developed. The present method may be of value because of the ready availability of the starting materials and the simplicity of the operations.

This work was supported in part by a Grant-in-Aid for Scientific Research (C) 22550035 from *Japan Society for the Promotion of Science*. We thank Mrs. *Miyuki Tanmatsu* of this university for recording mass spectra and performing combustion analyses.

Experimental Part

1. *General.* Aryl(2-isothiocyanatophenyl)methanones **1** were prepared according to the reported procedure [3]. BuLi was supplied by *Asia Lithium Corporation*. All other chemicals used in this study were commercially available. All of the org. solvents used were dried over the appropriate drying agents and distilled under Ar prior to use. TLC: *Merck* silica gel *60 PF_{254}*. Column chromatography (CC): *Wako Gel C-200E*. M.p.: *Laboratory-Devices-Mel-Temp-II* melting-point apparatus; uncorrected. IR Spectra: *Shimadzu-FTIR-8300* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra (500 or 400 MHz): *Jeol-ECP-500* FT NMR spectrometer or *Jeol-LA400* FT NMR spectrometer; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. ^{13}C-NMR (125 MHz): *Jeol-ECP-500* FT NMR spectrometer; δ in ppm rel. to Me_4Si as internal standard. MS (EI, 70 eV): *Jeol-JMS-AX-505-HA* spectrometer; in *m*/*z* (rel. %).

2. *(2*E*)-1-(2-Isothiocyanatophenyl)-3-phenylprop-2-en-1-one* (**3**). Compound **3** was prepared starting with (2*E*)-1-(2-aminophenyl)-3-phenylprop-2-en-1-one [4], *via N*-{2-[(2*E*)-1-oxo-3-phenylprop-2-en-1-yl]phenyl}formamide and (2*E*)-1-(2-isocyanophenyl)-3-phenylprop-2-en-1-one, followed by the sequence reported previously for the preparation of **1** [3].

N-*{2-[(2*E*)-1-Oxo-3-phenylprop-2-en-1-yl)phenyl}formamide:* Yield 74%. Yellow crystals. M.p. 132–135° (toluene). IR (KBr): 3179, 1690, 1634. ^{1}H-NMR (400 MHz): 7.22 (*t*, *J* = 7.3, 1 H); 7.45–7.65 (*m*, 8 H); 7.82 (*d*, *J* = 15.6, 1 H); 7.80 (*d*, *J* = 7.3, 1 H); 8.52–11.43 (*m*, 2 H). Anal. calc. for $C_{16}H_{13}NO_2$ (251.28): C 76.48, H 5.21, N 5.57; found: C 76.50, H 5.25, N 5.55.

*(2*E*)-1-(2-Isocyanophenyl)-3-phenylprop-2-en-1-one:* Yield 70%. Yellow solid. M.p. 81° (hexane/Et_2O, dec.). IR (KBr): 2124, 1645, 1601: ^{1}H-NMR (500 MHz): 7.26 (*d*, *J* = 16.0, 1 H); 7.40–7.45 (*m*, 3 H); 7.50–7.57 (*m*, 3 H); 7.58–7.64 (*m*, 3 H); 7.68 (*dd*, *J* = 7.3, 1.4, 1 H). Anal. calc. for $C_{16}H_{11}NO$ (233.26): C 82.38, H 4.75, N 6.00; found: C 82.31, H 4.76, N 5.75.

Compound **3**: Yield 69%. Orange solid. M.p. 85–87° (hexane/Et_2O). IR (KBr): 2106, 1667, 1645, 1604. ^{1}H-NMR (500 MHz): 7.27 (*d*, *J* = 13.3, 1 H); 7.36–7.44 (*m*, 5 H); 7.52 (*td*, *J* = 7.8, 1.4, 1 H); 7.62–7.68 (*m*, 4 H). Anal. calc. for $C_{16}H_{11}NOS$ (265.33): C 72.43, H 4.18, N 5.28; found: C 72.40, H 4.20, N 5.18.

3. *One-Pot Synthesis: General Procedure, Ethyl 1,4-Dihydro-4-phenyl-2-thioxo-2*H*-3,1-benzoxazine-4-acetate* (**2a**). To a stirred soln. of LDA (0.97 mmol), generated from BuLi and $(^iPr)_2NH$ by the standard method, in THF (2 ml) at −78° was added dropwise AcOEt (85 mg, 0.97 mmol). After 15 min, **1a**

(0.20 g, 0.97 mmol) in THF (2 ml) was added dropwise, and stirring was continued for an additional 10 min at −78°. Sat. aq. NH_4Cl (10 ml) was added and the mixture was extracted with AcOEt (3 × 10 ml). The combined extract was washed with brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (SiO_2): **2a** (0.22 g, 69%). Pale yellow amorphous powder. R_f (AcOEt/hexane 1:5) 0.16. IR (neat): 3219 1730, 1620, 1601. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.09 (*t*, *J* = 7.4, 3 H); 3.40 (*d*, *J* = 16.0, 1 H); 3.48 (*d*, *J* = 16.0, 1 H); 4.00–4.08 (*m*, 2 H); 6.91 (*d*, *J* = 8.0, 1 H); 7.30 (*t*, *J* = 7.4, 1 H); 7.23–7.50 (*m*, 7 H); 10.07 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 13.91; 45.04; 60.94; 86.67; 114.31; 122.90; 124.79; 125.51; 125.73; 128.64; 128.80; 129.61; 132.20; 140.83; 167.98; 183.35. MS: 327 (37, M^+), 240 (100). Anal. calc. for $C_{18}H_{17}NO_3S$ (327.40): C 66.03, H 5.23, N 4.28; found: C 55.84, H 5.19, N 4.44.

*1,1-Dimethylethyl 1,4-Dihydro-4-phenyl-2-thioxo-2*H-*3,1-benzoxazine-4-acetate* (**2b**): White solid. M.p. 143–145° (hexane/Et_2O). IR (KBr): 3181, 1727, 1620, 1157. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.26 (*s*, 9 H); 3.32 (*d*, *J* = 16.6, 1 H); 3.43 (*d*, *J* = 16.6, 1 H); 6.83 (*d*, *J* = 7.3, 1 H); 7.23 (*dd*, *J* = 7.8, 7.3, 1 H); 7.28–7.36 (*m*, 6 H); 7.40 (*d*, *J* = 7.8, 1 H); 9.13 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 27.70; 46.61; 81.55; 86.90; 114.25; 122.99; 124.77; 125.55; 125.70; 128.60; 128.69; 129.51; 132.06; 140.95; 167.22; 183.26. MS: 355 (41, M^+), 240 (100). Anal. calc. for $C_{20}H_{21}NO_3S$ (355.45): C 67.58, H 5.95, N 3.94; found: C 67.56, H 6.02, N 3.74.

*1,4-Dihydro-*N,N-*dimethyl-4-phenyl-2-thioxo-2*H-*3,1-benzoxazine-4-acetamid*e (**2c**): Pale yellow solid. M.p. 229–231° (THF). IR (KBr): 3173, 1630, 1174. ^{1}H-NMR (500 MHz, (D_6)DMSO): 2.72 (*s*, 3 H); 2.99 (*s*, 3 H); 3.36 (*d*, *J* = 17.2, 1 H); 3.71 (*d*, *J* = 17.2, 1 H); 6.96 (*d*, *J* = 8.0, 1 H); 7.13 (*t*, *J* = 7.4, 1 H); 7.24–7.36 (*m*, 6 H); 7.49 (*d*, *J* = 7.4, 1 H); 12.02 (br. *s*, 1 H). ^{13}C-NMR ((D_6)DMSO): 34.85; 36.86; 42.11; 86.25; 114.02; 123.95; 124.14; 125.40; 128.06; 128.39; 128.44; 132.08; 142.97; 166.89; 182.19. MS: 326 (100, M^+). Anal. calc. for $C_{18}H_{18}N_2O_2S$ (326.41): C 66.23, H 5.56, N 8.58; found: C 66.22, H 5.48, N 8.40.

*(1,4-Dihydro-4-phenyl-2-thioxo-2*H-*3,1-benzoxazin-4-yl)methyl](piperidin-1-yl)methanone* (**2d**): White solid. M.p. 209–213° (hexane/THF). IR (KBr): 3185, 1612, 1169. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.47–1.71 (*m*, 6 H); 3.43 (*d*, *J* = 15.5, 1 H); 3.46–3.62 (*m*, 5 H); 6.73 (*d*, *J* = 7.4, 1 H); 7.13 (*dd*, *J* = 8.0, 7.4, 1 H); 7.20 (*t*, *J* = 7.4, 1 H); 7.23–7.31 (*m*, 5 H); 7.66 (*d*, *J* = 8.0, 1 H); 9.84 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 24.37; 25.49; 26.49; 42.92; 43.08; 47.77; 88.00; 114.23; 123.07; 124.52; 125.55; 126.47; 128.45; 128.50; 129.25; 132.21; 141.70; 165.62; 183.19. MS: 366 (100, M^+). Anal. calc. for $C_{21}H_{22}N_2O_2S$ (366.48): C 68.82, H 6.05, N 7.64; found: C 68.74, H 6.05, N 7.59.

*[(1,4-Dihydro-4-phenyl-2-thioxo-2*H-*3,1-benzoxazin-4-yl)methyl](morpholin-4-yl)methanone* (**2e**): White solid. M.p. 233–235° (hexane/THF). IR (KBr): 3183, 1626, 1165. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.37–3.84 (*m*, 10 H); 6.75 (*d*, *J* = 7.8, 1 H); 7.27–7.34 (*m*, 7 H); 7.73 (*d*, *J* = 7.3, 1 H); 8.77 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 42.19; 42.86; 47.17; 66.76; 66.89; 88.06; 114.10; 122.69; 124.67; 125.41; 125.96; 126.64; 128.69 (2 C); 129.65; 141.36; 165.85; 183.14. MS: 368 (100, M^+). Anal. calc. for $C_{20}H_{20}N_2O_3S$ (368.45): C 65.20, H 5.47, N 7.60; found: C 65.18, H 5.47, N 7.50.

*Ethyl 6-Chloro-1,4-dihydro-4-phenyl-2-thioxo-2*H-*3,1-benzoxazine-4-acetate* (**2f**): Pale yellow solid. M.p. 166–169° (hexane/THF). IR (KBr): 3179, 1742, 1619, 1156. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.13 (*t*, *J* = 7.4, 3 H); 3.37 (*d*, *J* = 16.0, 1 H); 3.46 (*d*, *J* = 16.0, 1 H); 4.06 (*q*, *J* = 7.4, 2 H); 6.88 (*d*, *J* = 8.0, 1 H); 7.29–7.35 (*m*, 7 H); 9.5–10.5 (br., 1 H). ^{13}C-NMR ($CDCl_3$): 13.91; 44.83; 61.11; 86.34; 115.67; 124.61; 125.64 (2 C), 128.80; 129.07; 129.67; 130.00; 130.86; 140.11; 167.68; 182.95. MS: 361 (27, M^+), 274 (100). Anal. calc. for $C_{18}H_{16}ClNO_3S$ (361.84): C 59.75, H 4.46, N 3.87; found: C 59.65, H 4.47, N 3.65.

*[(6-Chloro-1,4-dihydro-4-phenyl-2-thioxo-2*H-*3,1-benzoxazin-4-yl)methyl](morpholin-4-yl)methanone* (**2g**): Pale yellow solid. M.p. 151–153° (hexane/THF). IR (KBr): 3187, 1626, 1165. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.45–3.94 (*m*, 10 H); 6.69 (*d*, *J* = 8.0, 1 H); 7.10 (*d*, *J* = 8.0, 1 H); 7.26–7.32 (*m*, 5 H); 7.80 (*s*, 1 H); 10.42 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 42.31; 42.74; 47.23; 66.66; 66.80; 87.64; 115.78; 124.39; 125.22; 126.54; 128.86 (2 C); 129.30; 129.68; 131.26; 141.04; 166.17; 182.60. MS: 402 (100, M^+). Anal. calc. for $C_{20}H_{19}ClN_2O_3S$ (402.89): C 59.62, H 4.75, N 6.95; found: C 59.42, H 4.69, N 6.90.

*1,1-Dimethylethyl 4-(4-Chlorophenyl)-1,4-dihydro-2-thioxo-2*H-*3,1-benzoxazine-4-acetate* (**2h**): Pale yellow solid. M.p. 168–170° (hexane/CH_2Cl_2). IR (KBr): 3188, 1728, 1620, 1602, 1158. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.27 (*s*, 9 H); 3.29 (*d*, *J* = 16.1, 1 H); 3.39 (*d*, *J* = 16.1, 1 H); 6.83 (*d*, *J* = 7.8, 1 H); 7.22–7.40 (*m*, 7 H); 8.98 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 27.73; 46.42; 81.76; 86.32; 114.35; 122.74; 124.92; 125.48; 127.32; 128.79; 129.78; 132.11; 134.80; 139.43; 166.96; 183.10. MS: 389 (60, M^+), 274 (100). Anal. calc. for $C_{20}H_{20}ClNO_3S$ (389.90): C 61.61, H 5.17, N 3.59; found: C 61.42, H 5.17, N 3.69.

4-(4-Chlorophenyl)-1,4-dihydro-N,N-*dimethyl-2-thioxo-2*H-*3,1-benzoxazine-4-acetamide* (**2i**): Pale yellow amorphous powder. R_f (THF/hexane 1:1) 0.41. IR (KBr): 3181, 1623, 1172. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.89 (*s*, 3 H); 3.13 (*s*, 3 H); 3.40 (*d*, *J* = 15.6, 1 H); 3.50 (*d*, *J* = 15.6, 1 H); 6.77 (*d*, *J* = 7.8, 1 H); 7.21 – 7.34 (*m*, 6 H); 7.57 (*d*, *J* = 7.8, 1 H); 9.03 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 35.77; 38.23; 43.15; 87.41; 114.23; 122.95; 124.78; 126.30; 127.31; 128.71; 129.57; 132.19; 134.66; 139.98; 167.05; 182.99. MS: 360 (100, M^+). Anal. calc. for $C_{18}H_{17}ClN_2O_2S$ (360.86): C 59.91, H 4.75, N 7.76; found: C 59.83, H 4.80, N 7.54.

*1,1-Dimethylethyl 1,4-Dihydro-4-(4-methoxyphenyl)-2-thioxo-2*H-*3,1-benzoxazine-4-acetat*e (**2j**): White solid. M.p. 163 – 164° (hexane/CH_2Cl_2). IR (KBr): 3182, 1719, 1620, 1171. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.26 (*s*, 9 H); 3.29 (*d*, *J* = 16.0, 1 H); 3.43 (*d*, *J* = 16.0, 1 H); 3.77 (*s*, 3 H); 6.83 (*d*, *J* = 8.6, 3 H); 7.20 (*d*, *J* = 8.6, 2 H); 7.21 (*dd*, *J* = 8.0, 7.4, 1 H); 7.33 (*dd*, *J* = 8.0, 7.4, 1 H); 7.36 (*d*, *J* = 8.0, 1 H); 9.11 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 27.73; 46.68; 55.24; 81.48; 86.84; 113.87; 114.20; 123.20; 124.68; 125.56; 127.25; 129.42; 132.15; 133.09; 159.71; 167.33; 183.30. MS: 385 (82, M^+), 270 (100). Anal. calc. for $C_{21}H_{23}NO_4S$ (385.48): C 65.43, H 6.01, N 3.63; found: C 65.19, H 6.03, N 3.88.

*Ethyl 1,4-Dihydro-4-[(1*E*)-2-phenylethenyl]-2-thioxo-2*H-*3,1-benzoxazine-4-acetat*e (**4a**): Yield 64%. Pale yellow solid. M.p. 143 – 146° (hexane/CH_2Cl_2). IR (KBr): 3201, 1749, 1625, 1168. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.15 (*t*, *J* = 7.3, 3 H); 3.26 (*d*, *J* = 16.1, 1 H); 3.32 (*d*, *J* = 16.1, 1 H); 4.05 – 4.10 (*m*, 2 H); 6.40 (*d*, *J* = 16.1, 1 H); 6.46 (*d*, *J* = 16.1, 1 H); 6.85 (*d*, *J* = 7.8, 1 H); 7.17 – 7.34 (*m*, 8 H); 9.07 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 13.98; 44.05; 61.01; 85.45; 114.25; 121.90; 124.88; 125.08; 127.01; 128.41; 128.61 (2 C); 129.59; 131.86; 132.61; 135.16; 168.01; 182.87. MS: 353 (67, M^+), 266 (100). Anal. calc. for $C_{20}H_{19}NO_3S$ (353.43): C 67.97, H 5.42, N 3.96; found: C 67.68, H 5.47, N 4.07.

*1,1-Dimethylethyl 2-{1,4-Dihydro-4-[(1*E*)-2-phenylethenyl]-2-thioxo-2*H-*3,1-benzoxazine-4-acetate* (**4b**): Yield 76%. White solid. M.p. 165 – 167° (hexane/CH_2Cl_2). IR (KBr): 3187, 1727, 1624, 1602, 1172. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.29 (*s*, 9 H); 3.18 (*d*, *J* = 16.1, 1 H); 3.27 (*d*, *J* = 16.1, 1 H); 6.37 (*d*, *J* = 16.1, 1 H); 6.43 (*d*, *J* = 16.1, 1 H); 6.88 (*d*, *J* = 7.8, 1 H); 7.17 – 7.32 (*m*, 8 H); 9.44 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 27.74; 45.61; 81.70; 85.76; 114.23; 121.89; 124.86; 125.05; 126.95; 128.51; 128.56; 128.72; 129.44; 131.74; 132.26; 135.13; 167.25; 182.74. Anal. calc. for $C_{22}H_{23}NO_3S$ (381.49): C 69.26, H 6.08, N 3.67; found; C 69.00, H 6.06, N 3.69.

1,4-Dihydro-N,N-*dimethyl-4-[(1*E*)-2-phenylethenyl]-2-thioxo-2*H-*3,1-benzoxazine-4-acetamide* (**4c**): Yield 77%. Pale yellow solid. M.p. 175 – 178° (hexane/CH_2Cl_2). IR (KBr): 3182, 1624, 1175. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.91 (*s*, 3 H); 3.09 (*s*, 3 H); 3.25 (*d*, *J* = 15.6, 1 H); 3.40 (*d*, *J* = 15.6, 1 H); 6.46 (*d*, *J* = 16.6, 1 H); 6.54 (*d*, *J* = 16.6, 1 H); 6.80 (*d*, *J* = 7.8, 1 H); 7.16 – 7.39 (*m*, 8 H); 9.04 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 35.75; 38.14; 42.46; 86.57; 114.12; 122.37; 124.96; 125.58; 126.99; 128.36; 128.53; 129.10; 129.27; 131.73; 131.78; 135.43; 157.41; 182.77. MS: 352 (100, M^+). Anal. calc. for $C_{20}H_{20}N_2O_2S$ (352.45): C 68.16, H 5.72, N 7.95; found: C 68.05, H 5.79, N 7.88.

REFERENCES

[1] a) A. Fensome, R. Bender, R. Chopra, J. Cohen, M. A. Collins, V. Hudak, K. Malakian, S. Lockhead, A. Olland, K. Svenson, E. A. Terefenko, R. J. Unwalla, J. M. Wilhelm, S. Wolfrom, Y. Zhu, Z. Zhang, P. Zhang, R. C. Winneker, J. Wrobel, *J. Med. Chem.* **2005**, *48*, 5092; b) J. C. Kern, E. A. Terefenko, A. Fensome, R. Unwallla, J. Wrobel, Y. Zhu, J. Cohen, R. Winneker, Z. Zhang, P. Zhang, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 189; c) H.-B. Zhou, J. H. Lee, C. G. Mayne, K. E. Carlson, J. A. Katzenellenbogen, *J. Med. Chem.* **2010**, *53*, 3349; d) T. Nariai, K. Fujita, M. Mori, S. Katayama, S. Hori, K. Matsui, *J. Pharmacol. Sci.* **2011**, *115*, 346.

[2] a) K. Kobayashi, Y. Yokoi, T. Komatsu, H. Konishi, *Tetrahedron* **2010**, *66*, 9336; b) K. Kobayashi, H. Hashimoto, Y. Kanbe, H. Konishi, *Tetrahedron* **2011**, *67*, 4535.

[3] K. Kobayashi, Y. Kanbe, *Tetrahedron* **2011**, *67*, 9680.

[4] J.-I. Lee, H.-J. Jung, *J. Korean Chem. Soc.* **2007**, *51*, 106.

Received February 28, 2012