Tetrahedron 67 (2011) 4535–4538

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

One-pot synthesis of 4-substituted 4-alkoxy-1,4-dihydro-3,1-benzoxazine-2-thiones by the reaction of 2-isothiocyanatobenzoates with organolithiums

Kazuhiro Kobayashi *, Hiroo Hashimoto, Yuuki Kanbe, 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

ARTICLE INFO

Article history:
Received 15 March 2011
Received in revised form 22 April 2011
Accepted 22 April 2011
Available online 5 May 2011

Keywords:
1,4-Dihydro-3,1-benzoxazine-2-thiones
2-Isothiocyanatobenzoates
Organolithiums
Lithium eater enolates
Lithium tertiary amide enolates

ABSTRACT

An efficient one-pot procedure for the preparation of 4-substituted 4-alkoxy-1,4-dihydro-3,1-benzoxazine-2-thiones from 2-isothiocyanatobenzoates has been developed. Thus, 2-isothiocyanatobenzoates were reacted with organolithiums including lithium enolates of acetates and tertiary acetamides in THF at −78 °C to give the desired products in generally good yields.

1. Introduction

Compounds having the 1,4-dihydro-3,1-benzoxazine-2-thione skeleton have recently attracted much attention, because some of these derivatives exhibit biological activities.[1] 1,4-Dihydro-3,1-benzoxazine-2-thione derivatives have been synthesized by the treatment of the respective 1,4-dihydro-3,1-benzoxazin-2-one with Lawesson reagent at rather higher temperatures.[1a,b,d] Therefore, we have recently reported a facile method for the preparation of 4-monosubstituted and 4,4-disubstituted derivatives by the reaction of 2-lithiophenyl isothiocyanates with aldehydes, ketones, or butanolide.[2] Literature searching revealed that there have been no reports on the synthesis of derivatives carrying an alkoxy substituent at the 4-position. In this paper, we wish to describe the results of our study on the reaction of 2-isothiocyanatobenzoates **1** with organolithiums including lithium enolates of acetates and tertiary acetamides, which provide facile access to 4-substituted 4-alkoxy-1,4-dihydro-3,1-benzoxazine-2-thiones **3**.

2. Results and discussion

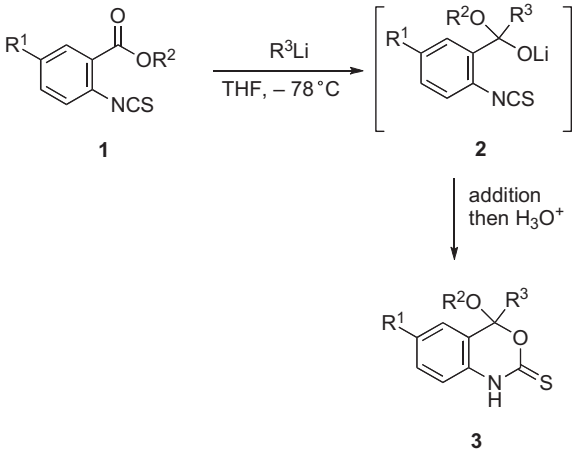
The starting isothiocyanates **1** were easily accessible. Methyl 2-isothiocyanatobenzoate (**1a**) and ethyl 2-isothiocyanatobenzoate (**1b**) were commercially available. Methyl 2-isothiocyanato-5-methoxybenzoate (**1c**) and ethyl 5-chloro-2-isothiocyanatobenzoate (**1d**) could be obtained in a three-step sequence from methyl 2-amino-5-methoxybenzoate[3] and ethyl-2-amino-5-chlorobenzoate,[4] respectively, utilizing the easily conducted reactions reported previously.[5–7]

First, we found that 2-isothiocyanatobenzoates **1** were allowed to react with various alkyl- or aryllithiums, including (thiophen-2-yl)lithium, in THF at −78 °C to give 4-substituted 4-alkoxy-1,4-dihydro-3,1-benzoxazines **3**. Probably almost completely selective addition of an organolithium to the ester carbonyl of **1** occurred to lead to formation of lithium 1-alkoxy-1-(isothiocyanatophenyl) alkan-1-yloxide intermediates **2**, which underwent cyclization by the attack of the alkanyloxide on the isothiocyanate carbon to give, after aqueous work up, products **3**, as illustrated in Scheme 1. These results are listed in Table 1, which indicates the yields of the products are relatively good. It is interesting to note that the addition of lithium 1-alkoxy-1-(isothiocyanatophenyl)alkan-1-yloxide to isothiocyanato functional group occurs before elimination of lithium alkoxide. This reaction sequence proceeded cleanly and was complete within 10 min. The structures of the products were determined on the basis of IR, ^{1}H and ^{13}C NMR, and MS spectroscopies and elemental analyses. For example, mass spectrometry and elemental analysis of the product **3a** indicated its molecular formula to be $C_{14}H_{19}NO_2S$. The IR spectrum showed no evidence for the presence of both the carbonyl and isothiocyanato groups but showed absorption bands at 3185 and 1186 cm^{-1} due to N–H and C=S groups, respectively. The ^{13}C NMR spectrum exhibited 14 signals including a signal at δ 183.26 assignable to the thiocarbonyl

* Corresponding author. Tel./fax: +81 857 31 5263; e-mail address: kkoba@chem.tottori-u.ac.jp (K. Kobayashi).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.04.088

carbon. The ^{1}H NMR spectrum exhibited a signal at δ 9.73 assignable to the N–H proton and the other signals were in good agreement with the structure of **3a**. The spectra for products **3b**–**f** uniformly showed the above characteristic signals in the same regions (see Experimental section).



1 **2** **3**

Scheme 1.

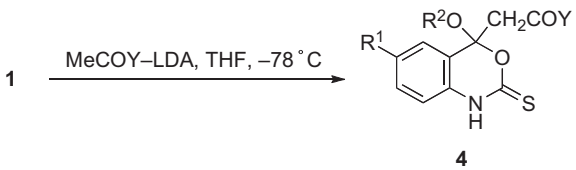
Table 1
Preparation of 4-alkoxy-1,4-dihydro-3,1-benzoxazine-2-thiones **3**

Entry	**1**	R^3	**3**	Yield[a]/%
1	**1a** (R^1=H, R^2=Et)	*n*-Bu	**3a**	76
2	**1b** (R^1=H, R^2=Me)	Ph	**3b**	75
3	**1c** (R^1=OMe, R^2=Me)	Me	**3c**	75
4	**1c**	*t*-Bu	**3d**	72
5	**1c**	Thiophen-2-yl	**3e**	82
6	**1d** (R^1=Cl, R^2=Et)	*n*-Bu	**3f**	81

[a] Isolated yields.

We next turned our attention to the use of lithium enolates of acetates and tertiary acetamides, which were generated from the respective acetates and tertiary acetamides using LDA under the standard conditions, in place of alkyl- or aryllithiums to obtain 2-methoxy-2-(2-thioxo-1,4-dihydro-3,1-benzoxazin-4-yl)acetic acid derivatives **4**. We found that the addition of lithium enolates to the ester carbonyl of **1** also occurred selectively and a reaction sequence similar to that described for the formation of **3** proceeded cleanly to give the desired products **4** as outlined in Scheme 2. Structure determination of the products **4** was carried out in a manner similar to that for the products **3** as mentioned above. The yields of the products were also relatively good as summarized in Table 2. An attempted use of 2-lithioacetonitrile proved unsuccessful, giving only a considerably intractable mixture of products.

Subsequently, the reaction of ethyl 2-isothiocyanatobenzoate (**1a**) and ethylmagnesium bromide under the same conditions as described for the reaction of **1a** with organolithiums was examined in order to explore the difference of the reactivities between these two organometals. The reaction resulted only in the formation of a rather intractable mixture of products, from which a 36% yield of ethyl 2-(thiopropanoylamino)benzoate (**5**) was obtained and no



4

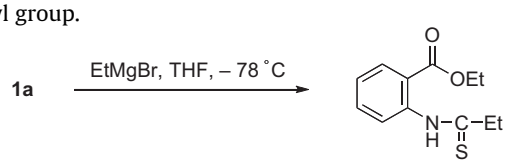
Scheme 2.

Table 2
Preparation of 2-(4-alkoxy-2-thioxo-1,4-dihydro-3,1-benzoxazin-4-yl)acetic acid derivatives **4**

Entry	**1**	Y	**4**	Yield[a]/%
1	**1a** (R^1=H, R^2=Et)	NMe_2	**4a**	63
2	**1a**	NEt_2	**4b**	70
3	**1a**	Pyrrolidin-1-yl	**4c**	64
4	**1a**	OEt	**4d**	76
5	**1b** (R^1=H, R^2=Me)	Piperidin-1-yl	**4e**	62
6	**1c** (R^1=OMe, R^2=Me)	OMe	**4f**	77
7	**1d** (R^1=Cl, R^2=Et)	O*t*-Bu	**4g**	91

[a] Isolated yields.

more than a trace amount of the corresponding 4-ethoxy-1,4-dihydro-3,1-benzoxazine-2-thione was obtained (Scheme 3). It may be speculated that a softer organometal, ethylmagnesium bromide, compared to organolithiums attacks preferentially the isothiocyanato group, which is a softer electrophilic group than the carbonyl group.



5 36%

Scheme 3.

In conclusion, the results reported above demonstrate that an efficient one-pot procedure has been developed for the preparation of 4-substituted 4-alkoxy-1,4-dihydro-3,1-benzoxazine-2-thiones by the reaction of 2-isothiocyanatobenzoates with organolithiums including lithium enolates of acetates and tertiary acetamides. It is unlikely that this type of 1,4-dihydro-3,1-benzoxazine-2-thiones can be prepared by previous methods.[1,2] The present method may find some value in organic synthesis, because it is operationally very simple and the starting materials are readily available.

3. Experimental

3.1. General

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer as KBr disks. ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a Bruker Biospin AVACNE II 600 spectrometer operating at 600 MHz, a JEOL ECP500 FT NMR spectrometer operating at 500 MHz, or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a Bruker Biospin AVACNE II 600 spectrometer operating at 150 MHz or a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured with a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Wako Gel C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

3.2. Starting materials

Methyl 2-amino-5-methoxybenzoate[3] and ethyl 2-amino-5-chlorobenzoate[4] were prepared by the reported procedure. All chemicals used in this study were commercially available.

3.2.1. 2-Formylaminobenzoates. The following formamides were prepared by the N-formylation of the respective 2-aminobenzoates with HCO_2H under the previously reported conditions.[5]

3.2.1.1. Methyl 2-formylamino-5-methoxybenzoate. Yield: 88%; a white solid; mp 61–64 °C (hexane–CH_2Cl_2); IR (KBr) 3287, 1705, 1686, 1667 cm^{-1}; ^1H NMR (500 MHz) δ 3.83 (s, 3H), 3.94 (s, 3H), 7.13 (dd, J=9.2, 3.4 Hz, 1H), 7.53 (d, J=3.4 Hz, 1H), 8.46 (d, J=1.7 Hz, 1H), 8.64 (d, J=9.2 Hz, 1H), 10.70 (br s, 1H). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.30; H, 5.40; N, 6.88.

3.2.1.2. Ethyl 5-chloro-2-formylaminobenzoate. Yield: 92%; a white solid; mp 119–120 °C (hexane–CH_2Cl_2); IR (KBr) 3282, 1702, 1686 cm^{-1}; ^1H NMR (400 MHz) δ 1.43 (t, J=7.3 Hz, 3H), 4.30 (q, J=7.3 Hz, 2H), 7.50 (dd, J=8.8, 2.4 Hz, 1H), 8.02 (d, J=2.4 Hz, 1H), 8.50 (d, J=1.5 Hz, 1H), 8.70 (d, J=8.8 Hz, 1H), 10.96 (br s, 1H). Anal. Calcd for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 52.61; H, 4.71; N, 6.11.

3.2.2. 2-Isocyanobenzoates. The following isocyanides were prepared by the dehydration of the above formamides with $POCl_3$ under the previously reported conditions.[6]

3.2.2.1. Methyl 2-isocyano-5-methoxybenzoate. Yield: 99%; a yellow solid; mp 58–59 °C (hexane–CH_2Cl_2); IR (KBr) 2131, 1732, 1607 cm^{-1}; ^1H NMR (500 MHz) δ 3.87 (s, 3H), 3.98 (s, 3H), 7.05 (dd, J=8.6, 2.9 Hz, 1H), 7.40 (d, J=8.6 Hz, 1H), 7.47 (d, J=2.9 Hz, 1H). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.61; H, 4.61; N, 7.14.

3.2.2.2. Ethyl 5-chloro-2-isocyanobenzoate. Yield: 89%; a pale-yellow solid; mp 85–86 °C (hexane–Et_2O); IR (KBr) 2136, 1736 cm^{-1}; ^1H NMR (400 MHz) δ 1.44 (t, J=7.3 Hz, 3H), 4.46 (q, J=7.3 Hz, 2H), 7.42 (d, J=8.3 Hz, 1H), 7.53 (dd, J=8.3, 2.4 Hz, 1H), 7.98 (d, J=2.4 Hz, 1H). Anal. Calcd for $C_{10}H_8ClNO_2$: C, 57.30; H, 3.85; N, 6.68. Found: C, 57.13; H, 3.87; N, 6.53.

3.2.3. 2-Isothiocyanatobenzoates. The following isothiocyanates were prepared by treating the above isocyanides with sulfur in the presence of a catalytic amount of selenium according to the procedure previously reported by Fujiwara et al.[7]

*3.2.3.1. Methyl 2-isothiocyanato-5-methoxybenzoate (**1c**).* Yield: 72%; a pale-yellow solid; mp 53–55 °C (hexane); IR (KBr) 2140, 1726 cm^{-1}; ^1H NMR (500 MHz) δ 3.85 (s, 3H), 3.98 (s, 3H), 7.03 (dd, J=8.6, 2.9 Hz, 1H), 7.22 (d, J=8.6 Hz, 1H), 7.47 (d, J=2.9 Hz, 1H). Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27. Found: C, 53.54; H, 4.28; N, 6.38.

*3.2.3.2. Ethyl 5-chloro-2-isothiocyanatobenzoate (**1d**).*[8] Yield: 81%; a white solid; mp 62–63 °C (hexane–Et_2O); IR (KBr) 2139, 1719 cm^{-1}; ^1H NMR (400 MHz) δ 1.44 (t, J=7.3 Hz, 3H), 4.23 (q, J=7.3 Hz, 2H), 7.24 (d, J=8.3 Hz, 1H), 7.47 (dd, J=8.3, 2.4 Hz, 1H), 7.96 (d, J=2.4 Hz, 1H).

3.3. Typical procedure for the preparation of 4-alkoxy-4-alkyl(or aryl)-1,4-dihydro-3,1-benzoxazine-2-thiones 3

*3.3.1. 4-Butyl-4-ethoxy-1,4-dihydro-3,1-benzoxazine-2-thione (**3a**).* To a stirred solution of **1a** (0.21 g, 1.0 mmol) in THF (4 mL) at −78 °C was added *n*-BuLi (1.6 M in hexane; 1.0 mmol) dropwise. Stirring was continued at the same temperature for 10 min before saturated aqueous NH_4Cl (10 mL) was added. The mixture was extracted with AcOEt three times (10 mL each), and the combined extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residual solid, which was recrystallized from hexane–CH_2Cl_2 to give **3a** (0.20 g, 76%); a white solid; mp 131–133 °C; IR (KBr) 3185, 1624, 1603, 1186 cm^{-1}; ^1H NMR (500 MHz) δ 0.84 (t, J=7.4 Hz, 3H), 1.18–1.46 (m, 7H), 2.03–2.09 (m, 1H), 2.14–2.20 (m, 1H), 3.37–3.43 (m, 1H), 3.59–3.65 (m, 1H), 6.90 (d, J=8.0 Hz, 1H), 7.20 (dd, J=8.0, 7.4 Hz, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.35 (ddd, J=8.0, 7.4, 1.1 Hz, 1H), 9.73 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.78, 14.94, 22.38, 25.01, 40.96, 60.06, 110.62, 114.08, 119.87, 125.30, 125.42, 130.29, 133.12, 183.26; MS m/z 265 (M^+, 33), 208 (100). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.18; H, 7.06; N, 5.20.

*3.3.2. 4-Methoxy-4-phenyl-1,4-dihydro-3,1-benzoxazine-2-thione (**3b**).* A white solid; mp 160–162 °C (hexane–$CHCl_3$); IR (KBr) 3173, 1620, 1603, 1157 cm^{-1}; ^1H NMR (400 MHz) δ 3.47 (s, 3H), 6.96 (d, J=7.8 Hz, 1H), 7.06 (dd, J=7.8, 1.0 Hz, 1H), 7.13 (ddd, J=7.8, 7.3, 1.0 Hz, 1H), 7.36 (ddd, J=7.8, 7.3, 1.0 Hz, 1H), 7.40–7.45 (m, 3H), 7.52 (dd, J=7.8, 1.5 Hz, 2H), 9.89 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 52.31, 107.95, 114.14, 121.46, 125.27, 126.68, 126.91, 128.51, 129.40, 130.56, 132.87, 137.67, 182.82; MS m/z 271 (M^+, 100). Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16. Found: C, 66.32; H, 4.83; N, 5.10.

*3.3.3. 4,6-Dimethoxy-4-methyl-1,4-dihydro-3,1-benzoxazine-2-thione (**3c**).* A pale-yellow solid; mp 157–158 °C (hexane–CH_2Cl_2); IR (KBr) 3181, 1622, 1184 cm^{-1}; ^1H NMR (500 MHz) δ 1.90 (s, 3H), 3.67 (s, 3H), 3.82 (s, 3H), 6.82 (d, J=2.3 Hz, 1H), 6.89 (d, J=8.6 Hz, 1H), 6.92 (dd, J=8.6, 2.3 Hz, 1H), 9.85 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.25, 51.46, 55.72, 107.18, 109.88, 115.62, 116.15, 122.32, 126.27, 157.36, 181.87; MS m/z 239 (M^+, 28) 224 (100). Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.03; H, 5.44; N, 5.52.

*3.3.4. 4,6-Dimethoxy-4-(1,1-dimethylethyl)-1,4-dihydro-3,1-benzoxazine-2-thione (**3d**).* A white solid; mp 173–178 °C (hexane–CH_2Cl_2); IR (KBr) 3188, 1612, 1172 cm^{-1}; ^1H NMR (500 MHz) δ 1.03 (s, 9H), 3.26 (s, 3H), 3.81 (s, 3H), 6.74 (d, J=2.9 Hz, 1H), 6.86 (d, J=9.2 Hz, 1H), 6.91 (dd, J=9.2, 2.9 Hz, 1H), 9.74 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.16, 43.40, 52.66, 55.70, 112.73, 115.24 (two overlapped Cs), 115.85, 118.15, 128.34, 156.48, 182.87; MS m/z 281 (M^+, 34), 224 (100). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found: C, 59.67; H, 6.82; N, 4.92.

*3.3.5. 4,6-Dimethoxy-4-(thiophen-2-yl)-1,4-dihydro-3,1-benzoxazine-2-thione (**3e**).* A pale-yellow solid; mp 121–123 °C (hexane–CH_2Cl_2); IR (KBr) 3185, 1616, 1165 cm^{-1}; ^1H NMR (500 MHz) δ 3.51 (s, 3H), 3.77 (s, 3H), 6.84 (d, J=2.8 Hz, 1H), 6.91 (d, J=8.6 Hz, 1H), 6.94 (dd, J=8.6, 2.8 Hz, 1H), 6.98 (dd, J=5.1, 3.4 Hz, 1H), 7.05 (dd, J=3.4, 1.1 Hz, 1H), 7.40 (dd, J=5.1, 1.1 Hz, 1H), 9.88 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.66, 55.74, 106.14, 110.84, 115.58, 116.84, 121.93, 126.70 (two overlapped Cs), 127.41, 127.84, 141.68, 157.29, 181.39; MS m/z 307 (M^+, 100). Anal. Calcd for $C_{14}H_{13}NO_3S_2$: C, 54.70; H, 4.26; N, 4.56. Found: C, 54.57; H, 4.48; N, 4.41.

*3.3.6. 4-Butyl-6-chloro-4-ethoxy-1,4-dihydro-3,1-benzoxazine-2-thione (**3f**).* A white solid; mp 180–181 °C (hexane–THF); IR (KBr) 3186, 1623, 1185 cm^{-1}; ^1H NMR (400 MHz) δ 0.86 (t, J=7.3 Hz, 3H), 1.21 (t, J=7.3 Hz, 3H), 1.24–1.36 (m, 4H), 1.99–2.06 (m, 1H), 2.11–2.19 (m, 1H), 3.40–3.47 (m, 1H), 3.59–3.67 (m, 1H), 6.87 (d, J=8.8 Hz, 1H), 7.23 (d, J=2.0 Hz, 1H), 7.32 (dd, J=8.8, 2.0 Hz, 1H), 9.86 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.80, 14.96, 22.38, 24.93, 40.70, 60.26, 109.99, 115.47, 121.72, 125.37, 130.47, 130.51, 131.70, 182.96; MS m/z 299 (M^+, 34), 242 (100). Anal. Calcd for $C_{14}H_{18}ClNO_2S$: C, 56.08; H, 6.05; N, 4.67. Found: C, 55.83; H, 6.02; N, 4.67.

3.4. Typical procedure for the preparation of 2-(2-thioxo-1,4-dihydro-3,1-benzoxazin-4-yl)acetic acid derivatives 4

*3.4.1. N,N-Dimethyl-2-(4-ethoxy-2-thioxo-1,4-dihydro-3,1-benzoxazin-4-yl)acetamide (**4a**).* To a stirred solution of LDA (1.2 mmol), generated by the standard method, in THF (5 mL) at −78 °C was

added $AcNMe_2$ (0.11 g, 1.2 mmol). After 15 min a solution of **1a** (0.25 g, 1.2 mmol) in THF (2 mL) was added and the stirring was continued for 30 min before saturated aqueous NH_4Cl (15 mL) was added. The mixture was extracted with AcOEt three times (10 mL each), and the combined extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent the residual solid was purified by recrystallization from hexane–$CHCl_3$ to give **4a** (0.22 g, 63%); a pale-yellow solid; mp 179–180 °C; IR (KBr) 3167, 1618, 1602, 1169 cm^{-1}; ^1H NMR (500 MHz) δ 1.18 (t, J=7.4 Hz, 3H), 2.84 (s, 3H), 3.05 (s, 3H), 3.20 (d, J=15.5 Hz, 1H), 3.24–3.29 (m, 1H), 3.38 (d, J=15.5 Hz, 1H), 3.54–3.59 (m, 1H), 6.81 (d, J=8.0 Hz, 1H), 7.15 (td, J=7.4, 1.1 Hz, 1H), 7.23 (dd, J=7.4, 1.1 Hz, 1H), 7.29 (ddd, J=8.0, 7.4, 1.1 Hz, 1H), 9.56 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 14.73, 34.49, 36.65, 43.43, 58.00, 105.62, 113.71, 119.42, 124.20, 125.02, 129.67, 133.88, 166.64, 181.28; MS m/z (%) 294 (M^+, 6.0), 249 (100). Anal. Calcd for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52. Found: C, 56.95; H, 6.21; N, 9.48.

*3.4.2. 2-(4-Ethoxy-2-thioxo-1,4-dihydro-3,1-benzoxazin-4-yl)-N, N-diethylacetamide (**4b**).* A white solid; mp 151–152 °C (hexane–CH_2Cl_2); IR (KBr) 3196, 1624, 1604, 1172 cm^{-1}; ^1H NMR (500 MHz_3) δ 1.01 (t, J=7.4 Hz, 3H), 1.18 (t, J=6.9 Hz, 6H), 3.18 (d, J=15.5 Hz, 1H), 3.18–3.35 (m, 4H), 3.35 (d, J=15.5 Hz, 1H), 3.39–3.46 (m, 1H), 3.54–3.60 (m, 1H), 6.79 (d, J=8.0 Hz, 1H), 7.16 (ddd, J=8.0, 7.4, 1.1 Hz, 1H), 7.24 (d, J=8.0 Hz, 1H), 7.30 (ddd, J=8.0, 7.4, 1.1 Hz, 1H), 9.41 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.83, 14.24, 14.79, 40.23, 42.36, 45.19, 59.64, 107.49, 114.11, 119.16, 124.77, 125.23, 130.20, 133.63, 165.97, 182.38; MS m/z 322 (M^+, 8.2), 277 (100). Anal. Calcd for $C_{16}H_{22}N_2O_3S$: C, 59.60; H, 6.88; N, 8.69. Found: C, 59.54; H, 6.95; N, 8.59.

*3.4.3. 2-(4-Ethoxy-2-thioxo-1,4-dihydro-3,1-benzoxazin-4-yl)-1-(pyrrolidin-1-yl)ethanone (**4c**).* A white solid; mp 158–161 °C (hexane–CH_2Cl_2); IR (KBr) 3171, 1614, 1601, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (t, J=6.9 Hz, 3H), 1.74–2.02 (m, 4H), 3.11 (d, J=15.5 Hz, 1H), 3.27–3.44 (m, 5H), 3.55–3.61 (m, 2H), 6.78 (d, J=8.0 Hz, 1H), 7.16 (td, J=7.4, 1.1 Hz, 1H), 7.26 (d, J=7.4 Hz, 1H), 7.30 (ddd, J=8.0, 7.4, 1.1 Hz, 1H), 9.29 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.81, 24.28, 26.07, 45.83, 46.91, 47.16, 59.62, 107.37, 114.29, 119.04, 124.77, 125.23, 130.24, 133.72, 165.36, 182.31; MS m/z 320 (M^+, 6.5), 275 (100). Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 59.90; H, 6.40; N, 8.52.

*3.4.4. Ethyl 2-(4-ethoxy-2-thioxo-1,4-dihydro-3,1-benzoxazin-4-yl) acetate (**4d**).* A white solid; mp 84–87 °C (hexane–CH_2Cl_2); IR (KBr) 3194, 1738, 1622, 1605, 1161 cm^{-1}; ^1H NMR (500 MHz) δ 1.11 (t, J=7.4 Hz, 3H), 1.18 (t, J=7.4 Hz, 3H), 3.19 (d, J=16.6 Hz, 1H), 3.28–3.34 (m, 2H), 3.55–3.61 (m, 1H), 3.97–4.03 (m, 2H), 6.91 (d, J=7.4 Hz, 1H), 7.19 (td, J=7.4, 1.1 Hz, 1H), 7.27 (dd, J=8.0, 1.1 Hz, 1H), 7.36 (ddd, J=8.0, 7.4, 1.1 Hz, 1H), 9.95 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.87, 14.78, 46.50, 59.83, 60.91, 106.22, 113.88, 118.59, 125.26, 125.40, 130.68, 133.37, 167.57, 182.53; MS m/z 295 (M^+, 5.4), 250 (100). Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.82; H, 5.94; N, 4.52.

*3.4.5. 2-(4-Methoxy-2-thioxo-1,4-dihydro-3,1-benzoxazin-4-yl)-1-(piperidin-1-yl)ethanone (**4e**).* A pale-yellow solid; mp 154–156 °C (hexane–CH_2Cl_2); IR (KBr) 3198, 1647, 1624, 1601, 1171 cm^{-1}; ^1H NMR (600 MHz) δ 1.45–1.61 (m, 6H), 3.20 (s, 3H), 3.26 (d, J=15.4 Hz, 1H), 3.38 (d, J=15.4 Hz, 1H), 3.40–3.51 (m, 4H), 6.86 (d, J=7.9 Hz, 1H), 7.15 (td, J=7.5, 1.0 Hz, 1H), 7.25 (d, J=7.5 Hz, 1H), 7.27 (ddd, J=7.9, 7.5, 1.0 Hz, 1H), 10.33 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.36, 25.42, 26.31, 42.76, 44.66, 47.27, 51.22, 107.58, 114.27, 118.45, 124.84, 125.36, 130.37, 133.80, 165.11, 182.36; MS m/z 320 (M^+, 5.8), 289 (100). Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 59.82; H, 6.40; N, 8.51.

*3.4.6. Methyl 2-(4,6-dimethoxy-2-thioxo-1,4-dihydro-3,1-benzoxazin-4-yl)acetate (**4f**).* A white solid; mp 171–173 °C (hexane–CH_2Cl_2); IR (KBr) 3198, 1740, 1631, 1609, 1163 cm^{-1}; ^1H NMR (600 MHz) δ 3.18 (d, J=16.0 Hz, 1H), 3.25 (s, 3H), 3.30 (d, J=16.0 Hz, 1H), 3.59 (s, 3H), 3.81 (s, 3H), 6.77 (d, J=2.9 Hz, 1H), 6.87 (d, J=8.6 Hz, 1H), 6.92 (dd, J=8.6, 2.9 Hz, 1H), 9.79 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.75, 51.35, 51.96, 55.70, 106.23, 110.11, 115.47, 116.69, 118.98, 127.31, 157.26, 167.99, 181.45; MS m/z 297 (M^+, 5.8), 266 (100). Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.51; H, 5.09; N, 4.71. Found: C, 52.33; H, 5.19; N, 4.49.

*3.4.7. 1,1-Dimethylethyl 2-(6-chloro-4-ethoxy-2-thioxo-1,4-dihydro-3,1-benzoxazin-4-yl)acetate (**4g**).* A white solid; mp 158–159 °C (hexane–CH_2Cl_2); IR (KBr) 3185, 1724, 1619, 1170 cm^{-1}; ^1H NMR (500 MHz) δ 1.19 (t, J=6.9 Hz, 3H), 1.29 (s, 9H), 3.09 (d, J=15.5 Hz, 1H), 3.26 (d, J=15.5 Hz, 1H), 3.33–3.39 (m, 1H), 3.55–3.61 (m, 1H), 6.87 (d, J=8.6 Hz, 1H), 7.27 (d, J=2.3 Hz, 1H), 7.33 (dd, J=8.6, 2.3 Hz, 1H), 9.99 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.79, 27.75, 47.50, 59.94, 82.01, 105.82, 115.25, 120.54, 125.50, 130.37, 130.76, 131.86, 166.41, 182.14; MS m/z 357 (M^+, 7.0), 312 (24), 301 (100). Anal. Calcd for $C_{16}H_{20}ClNO_4S$: C, 53.70; H, 5.63; N, 3.91. Found: C, 53.68; H, 5.69; N, 3.87.

3.5. Ethyl 2-(thiopropanoylamino)benzoate (5)[9]

To a stirred solution of **1a** (0.21 g, 1.0 mmol) in THF (4 mL) at −78 °C was added EtMgBr (3 M in Et_2O; 1.0 mmol) dropwise. After 20 min saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with AcOEt three times (10 mL each). The combined extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residue was purified by preparative TLC on silica gel to give **5** (86 mg, 36%); a yellow oil; R_f 0.16 (hexane); IR (neat) 3250, 1694, 1609, 1263 cm^{-1}; ^1H NMR (500 MHz) δ 1.428 and 1.433 (2t, J=7.8 and 6.8, respectively, combined 6H), 2.92 (q, J=7.8 Hz, 2H), 4.41 (q, J=6.8 Hz, 2H), 7.23 (dd, J=8.8, 7.8 Hz, 1H), 7.60 (ddd, J=8.8, 7.8, 2.0 Hz, 1H), 8.10 (d, J=7.8 Hz, 1H), 9.54 (d, J=8.8 Hz, 1H), 12.39 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.77, 14.14, 43.79, 61.74, 117.64, 121.54, 124.63, 130.91, 133.72, 141.59, 168.08, 206.34; MS m/z 237 (M^+, 100).

Acknowledgements

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

References and notes

1. (a) Fensome, A.; Bender, R.; Chopra, R.; Cohen, J.; Collins, M. A.; Hudak, V.; Malakian, K.; Lockhead, S.; Olland, A.; Svenson, K.; Terefenko, E. A.; Unwalla, R. J.; Wilhelm, J. M.; Wolform, S.; Zhu, Y.; Zhang, Z.; Zhang, P.; Winneker, R. C.; Wrobel, J. *J. Med. Chem.* **2005**, *48*, 5092–5095; (b) Kern, J. C.; Terefenko, E. A.; Fensome, A.; Unwallla, R.; Wrobel, J.; Zhu, Y.; Cohen, J.; Winneker, R.; Zhang, Z.; Zhang, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 189–192; (c) Nakagawa, A.; Uno, S.; Makishima, M.; Miyachi, H.; Hashimoto, Y. *Bioorg. Med. Chem.* **2008**, *16*, 7046–7054; (d) Zhou, H.-B.; Lee, J. H.; Mayne, C. G.; Carson, K. E.; Katzenellenbogen, J. A. *J. Med. Chem.* **2010**, *53*, 3349–3360.
2. Kobayashi, K.; Yokoi, Y.; Komatsu, T.; Konishi, H. *Tetrahedron* **2010**, *66*, 9336–9339.
3. Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017–3035.
4. Kobayashi, K.; Takanohashi, A.; Hashimoto, K.; Morikawa, O.; Konishi, H. *Tetrahedron* **2006**, *62*, 3158–3161.
5. Kobayashi, K.; Yoneda, K.; Miyamoto, K.; Morikawa, O.; Konishi, H. *Tetrahedron* **2004**, *60*, 11639–11645.
6. Ito, Y.; Kobayashi, K.; Seko, N.; Saegusa, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73–84.
7. Fujiwara, S.; Shin-Ike, T.; Sonoda, N.; Aoki, M.; Okada, K.; Miyoshi, N.; Kambe, N. *Tetrahedron Lett.* **1991**, *32*, 3503–3506.
8. Venugopalan, B.; Bapat, C. P.; Kaenik, P. J.; Chatterjee, D. K.; Iyer, N.; Lepcha, D. *J. Med. Chem.* **1995**, *38*, 1922–1927.
9. Clausen, K.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1979**, *88*, 305–311.