Notes

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Synthesis of 3-Substituted Benzoxazoline-2-thiones

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Several methods for the preparations of 3-substituted benzoxazoline-2-thiones (**1**) were examined. Method B *via* the thiation of 3-substituted benzoxazolin-2-one (**5**) with phosphorus pentasulfide was found to be applicable to the preparation of most analogs of **1**, with a few exceptions. Method C *via* the cyclization of 2-(alkylamino)phenol (**7**) with potassium *O*-methyldithiocarbonate was suitable for the preparation of analogs with a group sensitive to high temperature or with an aryl- (including aromatic heterocyclic ring) methyl group.

In addition, the reaction of benzoxazoline-2-thione (**2**) with acetals such as 1-ethoxyisochroman, 2-ethoxytetrahydrofuran, and 2-ethoxytetrahydropyran, or with Michael acceptors such as 2,3-dihydrofuran and 2*H*-3,4-dihydropyran, gave 3-substituted benzoxazoline-2-thione (**1d**—**f**).

Keywords——3-substituted benzoxazoline-2-thione; 3-substituted benzoxazolin-2-one; 2-(alkylthio)benzoxazole; 2-(alkylamino)phenol; acetal; Michael acceptor; thiation; UV spectra

Benzoxazoline-2-thiones have been reported to exhibit diverse biological properties. In particular, 3-methyl and 3-ethylbenzoxazoline-2-thiones were reported to have fungicidal activity.[1] Furthermore, 3-(*N*-substituted aminomethyl)benzoxazoline-2-thiones display bacteriocidal[1b,2] and spasmolytic[3] activities. However, there have been few reports on the preparation of benzoxazoline-2-thiones[2,3] with a substituent other than acyl, *N*,*N*-dialkylaminomethyl, methyl, or ethyl at position 3. These facts prompted us to search for a general method for the preparation of **1** with a variety of substituents at position 3.

Three possible methods (A, B, and C) for the preparation of **1** (shown in Chart 1) were examined. At first, 3-benzylbenzoxazoline-2-thione (**1c**) was prepared by these methods in order to compare them. The overall yields of **1c** from 2-aminophenol were 60 (method A), 50 (method B), and 81% (method C).

Method A involves an alkylation process of benzoxazoline-2-thiones (**2**). The alkylation of **2** with several alkylating agents, such as diazomethane,[4] dimethyl sulfate,[4,5] or alkyl halides with a phase transfer catalyst,[6] has been found to give 2-(alkylthio)benzoxazole (**3**) as the main product.

However, in our present investigation, some analogs of **1** were found to be obtained from **2**. The reaction of **2** with *tert*-butyl bromide gave 3-*tert*-butylbenzoxazoline-2-thione (**1b**) in higher yield (19%) than that (5%) of 2-(*tert*-butylthio)benzoxazole[7] (**3b**). On the basis of the previous finding that 1-ethoxyisochroman readily reacted with the nitrogen atom of acetamide to give 1-acetamidoisochroman,[8] the reaction of **2** with 1-ethoxyisochroman was examined. 3-(1-Isochromanyl)benzoxazoline-2-thione (**1d**) was obtained in 85% yield. This result suggested that acetals, such as 2-ethoxytetrahydrofuran and 2-ethoxytetrahydropyran, may react with **2** to give the corresponding 3-substituted benzoxazoline-2-thiones. Actually, 3-(2-tetrahydrofuryl)benzoxazoline-2-thione (**1e**) and 3-(2-tetrahydropyranyl)benzoxazoline-2-thione (**1f**) were obtained in 52 and 75% yields, respectively. Compounds **1e** and **f** were also

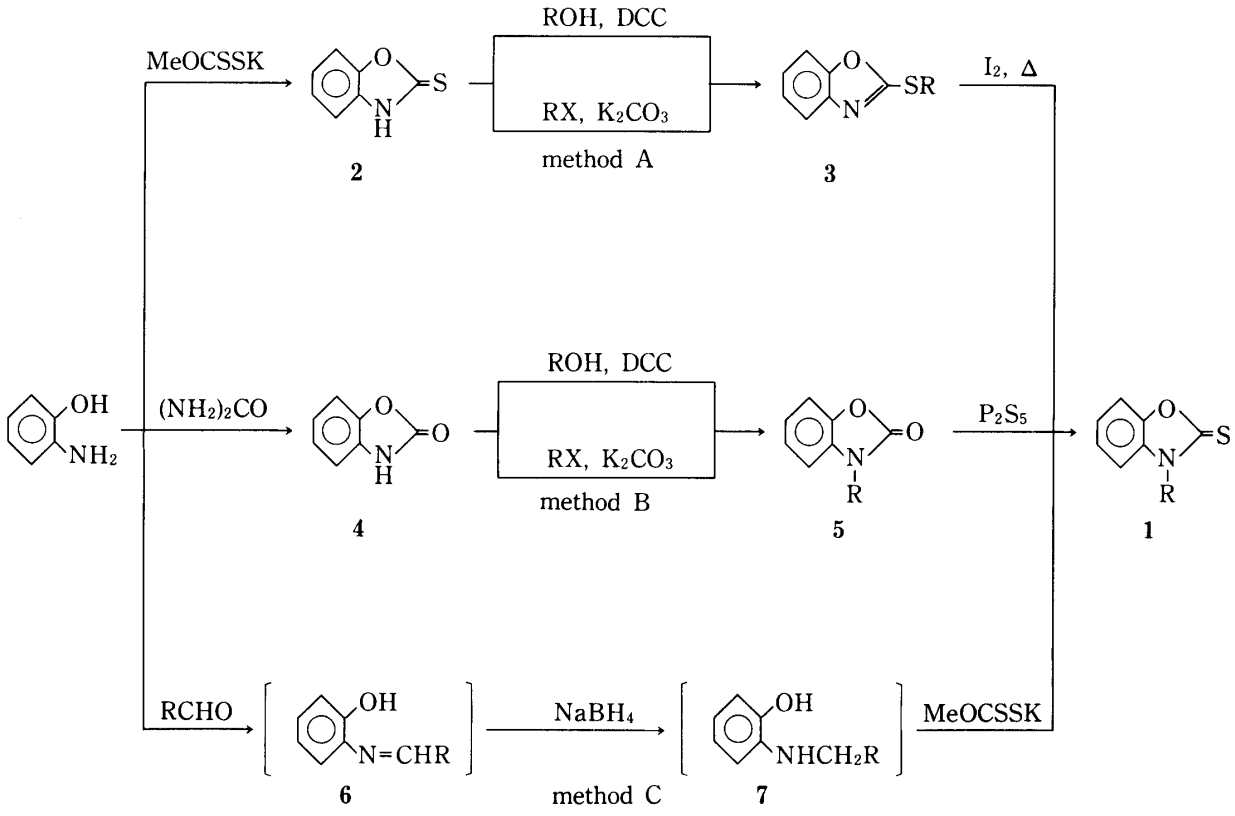


Chart 1

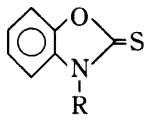
prepared by the reaction of **2** with Michael acceptors, 2,3-dihydrofuran and 2*H*-3,4-dihydropyran, in 57 and 59% yields, respectively. The structures of **1d—f** were determined by ultraviolet (UV) spectrometry. Namely, it is known that UV absorption maxima of 3-substituted benzoxazoline-2-thiones (**1**) appear in the region of 309 nm and that UV spectra of 2-substituted benzoxazoles (**3**) give two absorption maxima in the regions of 280 and 290 nm (Table I).

Method B involves an alkylation process of benzoxazolin-2-ones (**4**) to give 3-alkylbenzoxazolin-2-ones (**5**). It is known that the reaction of **4** with alkylating agents, such as alkyl halides,[9] dialkyl oxalates,[10] dialkyl sulfates,[11] or alkyl toluenesulfonates,[12] gives **5**. However, in our present experiment, these procedures did not give a satisfactory yield of **5** having a long carbon chain at position 3. We succeeded in the synthesis of **5** having such an alkyl group at position 3 by heating a mixture of **4** and 2-alkyl-1,3-dicyclohexylisourea. The resulting **5** was converted to **1** by heating with phosphorus pentasulfide in a mixture of xylene and hexamethylphosphorus triamide (HMPT).

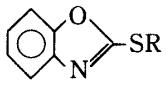
Method C involves an alkylation process of 2-aminophenol to give 2-(alkylamino)phenols (**7**). Compound **6** was prepared by the reaction of the Schiff base, formed from 2-aminophenol and aldehydes, with sodium borohydride ($NaBH_4$); it was immediately converted to **1** by reaction with potassium *O*-methyldithiocarbonate because of its instability in air.

Although these three methods seemed to be equally applicable to the preparation of **1** with various substituents at position 3, each of these methods was found to have defects. For example, 3-furfurylbenzoxazoline-2-thione (**1g**) could not be prepared by methods A and B but was obtained in 41% yield by method C: on heating of 2-(furfurylthio)benzoxazole (**3g**) at 180°C in the presence of small pieces of iodine (method A), rearrangement of the furfuryl group did not occur and polymeric products were obtained. In method B, the yields of 3-furfurylbenzoxazolin-2-one (**5g**) in the reactions of **4** with furfuryl alcohol and dicyclohexyl-

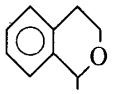
TABLE I. UV Data for **1** and **3**



1



3

	R	UV $\lambda_{max}^{CHCl_3}$ nm (log ε)	
		1	**3**
a	CH_3–	309 (4.48)	280 (4.13), 288 (4.12)
b	*tert*-C_4H_9–	308 (4.45)	281 (4.03), 288 (4.05)
c	$C_6H_5CH_2$–	309 (4.50)	282 (4.21), 289 (4.21)
d		302 (4.46)	——
e		304 (4.47)	——
f		303 (4.46)	——

carbodiimide (DCC) or with furfuryl chloride were poor (5%). For another example, rearrangement of the hexyl group of 2-(1-hexylthio)benzoxazole (**3h**), prepared from **3** and 1-hexyl chloride (method A), did not succeed and the starting material was recovered. Moreover, the preparation of 3-(1-hexyl)benzoxazoline-2-thione (**1h**) by method C failed. However, **1c** was obtained by method B in 50% yield.

In summary, the applicability of method A was found to be limited to the preparation of special analogs of **1** with a substituent such as methyl or benzyl at position 3, which could readily rearrange. Method B was better for the preparation of most analogs of **1** with a few exceptions, such as **1b**. Method C was suitable for the preparation of analogs of **1** with a group sensitive to high temperature (which is required in method A), or analogs of **1** with an aryl-(including heterocyclic ring) methyl group.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken with a Hitachi R-24 spectrometer at 60 MHz, with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 spectrometer. UV spectra were taken with Shimadzu UV-180 spectrometer.

General Procedure of Method A. A Typical Example: 3-Benzylbenzoxazoline-2-thione (1c)——i) 2-(Benzylthio)benzoxazole (**3c**) was prepared by the following methods (a and b). Method a: A solution of benzyl alcohol (5 g), DCC (10 g), and Cu_2Cl_2 (a catalytic amount) in dimethylformamide (DMF) (100 ml) was stirred at room temperature overnight. Benzoxazoline-2-thione[13] (**2**, 7 g) was then added to the solution and the mixture was stirred at room temperature for 1 h. The filtrate was concentrated and the residue was chromatographed on a column of alumina with cyclohexane to give 8 g (72%) of **3c**, mp 47—48°C (lit.,[14] 51—52°C).

Method b: A solution of **2** (4 g), benzyl chloride (5 g), and K_2CO_3 (6 g) in DMF (100 ml) was stirred at room temperature for 1 h. The filtrate was concentrated and the residue was chromatographed on a column of alumina with cyclohexane to give 4.8 g (75%) of **3c**, which was identical with the authentic sample prepared by method a.

ii) Compound **3c** was heated at 180°C for 12 h in the presence of small pieces of iodine and the resulting product was recrystallized from benzene to give 1.2 g (60%) of **1c**, mp 167—169.5°C. *Anal.* Calcd for $C_{14}H_{11}NOS$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.83; H, 4.59; N, 5.58. NMR ($CDCl_3$) δ: 5.46 (2H, s, CH_2). MS *m/e*: 241 (M^+).

Similarly, 3-methylbenzoxazoline-2-thione[15] (**1a**) was prepared from 2-(methylthio)benzoxazole[5b] (**3a**) in 53% yield.[16]

General Procedure of Method B. A Typical Example: **1a**——i) 3-Benzylbenzoxazolin-2-one (**5c**) was prepared by the following methods (a and b). Method a: A mixture of benzyl alcohol (3.2 g), DCC (4.9 g), Cu_2Cl_2 (a catalytic amount), and dry tetrahydrofuran (THF) (50 ml) was stirred at room temperature overnight, then benzoxazolin-2-one[17] (**4**, 4 g) was added and the solvent was evaporated off. The residue was further heated at 150°C for 6 h and dissolved in CH_2Cl_2. The CH_2Cl_2 layer was washed with 10% KOH and H_2O, dried, and concentrated. The residue was recrystallized from benzene to give 5.2 g (78%) of **5c**, mp 130°C (lit.,[18] 127°C).

Method b: Benzyl chloride (2 g) was added to a mixture of **4** (2 g), K_2CO_3 (2 g), and DMF (100 ml). The mixture was then heated at 60°C for 2.5 h and poured into ice-water. The resulting precipitate was recrystallized to give 2.6 g (78%) of **5a**, mp 128—130°C, which was identical with the authentic sample prepared by method a.

Similarly, 3-(1-hexyl)benzoxazolin-2-one (**5h**) was prepared in 54% yield, as an oil, bp 155—160°C (1—2 mmHg). *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 70.90; H, 7.82; N, 6.39. Found: C, 70.82; H, 8.07; N, 6.13. NMR ($CDCl_3$) δ: 0.74—2.09 [11H, m, $(CH_2)_4CH_3$], 3.25 (2H, t, J=7 Hz, NCH_2). MS *m/e*: 219 (M^+).

ii) A solution of **5c** (0.67 g) and P_2S_5 (1.4 g) in HMPT (15 ml) was heated at 120°C for 6 h and poured into NH_3 aq. (50 ml). The mixture was extracted with Et_2O and the Et_2O layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was recrystallized from benzene to give 0.38 g (53%) of **1c**, mp 167—169°C, which was identical with an authentic sample.

Similarly, 3-(1-hexyl)benzoxazoline-2-thione was prepared in 50% yield, mp 66—68°C (from cyclohexane). *Anal.* Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95. Found: C, 65.85; H, 7.40; N, 5.72. NMR ($CDCl_3$) δ: 0.64—2.13 [11H, m, $(CH_2)_4CH_3$], 3.82 (2H, t, J=7 Hz, NCH_2). MS *m/e*: 235 (M^+).

General Procedure of Method C. A Typical Example: **1a**——2-Aminophenol (3 g) was added portionwise to a mixture of benzaldehyde (3.6 g) and methanol (180 ml). The mixture was stirred at room temperature overnight, then $NaBH_4$ (2.1 g) was gradually added with cooling. After the mixture had been stirred at room temperature for 0.5 h, CS_2 (10 g) and KOH (5 g) were added. The mixture was then allowed to reflux for 30 h and poured into ice-water. The resulting precipitate was washed with 10% HCl and recrystallized from cyclohexane to give 5.4 g (81%) of **1c**, which was identical with an authentic sample.

Similarly, 3-furfuryl (**1g**), 3-(4-*N*,*N*-dimethylaminobenzyl)- (**1k**), 3-(2,4-dimethoxybenzyl)- (**1m**), and 5-chloro-3-(2-thienylmethyl)- (**1m**) benzoxazoline-2-thiones were prepared. **1g**: Yield 41%. mp 103—103.5°C (from benzene–cyclohexane). *Anal.* Calcd for $C_{12}H_9NO_2S$: C, 62.34; H, 3.92; N, 5.06. Found: C, 62.18; H, 3.80; N, 5.88. NMR ($CDCl_3$) δ: 5.38 (2H, s, NCH_2). MS *m/e*: 231 (M^+). **1k**: Yield 42%. mp 159—161°C (from THF–MeOH). *Anal.* Calcd for $C_{16}H_{16}N_2OS$: C, 67.57; H, 5.67; N, 9.85. Found: C, 67.27; H, 5.55; N, 9.64. NMR (DMSO-d_6) δ: 2.89 (6H, s, $CH_3\times2$), 5.40 (2H, s, NCH_2). MS *m/e*: 284 (M^+). **1m**: Yield, 19%. mp 134—135°C (from benzene–cyclohexane). *Anal.* Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.01; N, 4.65. Found: C, 64.13; H, 4.90; N, 4.45. NMR (DMSO-d_6) δ: 3.75 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.37 (2H, s, NCH_2). MS *m/e*: 301 (M^+).

3-(1-Isochromanyl)benzoxazoline-2-thione (**1d**)——A solution of **2** (4.5 g) and 1-ethoxyisochroman (7 g) in xylene (50 ml) was allowed to reflux for 1 h in an Ar atmosphere while the xylene and the EtOH formed were distilled off. The xylene was then completely removed under reduced pressure and the residue was recrystallized from AcOEt–petr. ether (1: 2) to give 7.1 g (85%) of **1d**, mp 126—126.5°C. *Anal.* Calcd for $C_{16}H_{13}NO_2S$: C, 67.84; H, 4.63; N, 4.95. Found: C, 67.84; H, 4.52; N, 4.78. NMR ($CDCl_3$) δ: 2.60—3.53 (2H, m, $C_4'H_2$), 3.38—4.40 (2H, m, $C_3'H_2$). MS *m/e*: 283 (M^+).

3-(2-Tetrahydrofuryl)benzoxazoline-2-thione (**1e**)——Method a: A solution of **2** (2 g) and 2-ethoxytetrahydrofuran (4.5 g) in xylene (150 ml) was heated at 150°C for 36 h in an autoclave, then concentrated. The residue was chromatographed on a column of alumina with AcOEt–petr. ether (1: 30) to give 1.5 g (52%) of **1e**, mp 56—58°C. *Anal.* Calcd for $C_{11}H_{11}N_2O_2S$: C, 59.72; H, 4.98; N, 6.33. Found: C, 59.98; H, 5.01; N, 6.39. NMR ($CDCl_3$) δ: 2.01—2.69 (4H, m, $C_3'H_2$ and $C_4'H_2$, 3.87—4.61 (2H, m, $C_5'H_2$), 6.40—6.69 (1H, m, $C_2'H$). MS *m/e*: 221 (M^+).

Method b: A solution of **2** (5 g) and 2,3-dihydrofuran (5 g) in pyridine (80 ml) was heated at 150°C for 12 h in an autoclave, then concentrated. The residue was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography on alumina with benzene, and the product was recrystallized from benzene–cyclohexane to give 4.2 g (57%) of **1e**, mp 56—58°C, which was identical with the authentic sample prepared by method a.

3-(2-Tetrahydropyranyl)benzoxazoline-2-thione (**1f**)——Method a: A solution of **2** (2 g) and 2-ethoxytetrahydropyran (5.2 g) in xylene (80 ml) was heated at 150°C for 36 h in an autoclave, then concentrated. The residue was chromatographed on a column of alumina with AcOEt–petr. ether (1: 15) to give 2.2 g (71%) of **1f**, as a viscous oil. *Anal.* Calcd for $C_{12}H_{13}NO_2S$: C, 61.28; H, 5.53; N, 5.96. Found: C, 61.39; H, 5.60; N, 6.01. NMR ($CDCl_3$) δ: 1.42—2.20 (6H, m, $C_3'H_2$, $C_4'H_2$, and $C_5'H_2$), 3.44—4.43 (2H, m, $C_6'H_2$), 5.89—6.35 (1H, m, $C_2'H$). MS *m/e*: 235 (M^+).

Method b: A solution of **2** (2 g) and 2*H*-3,4-dihydropyran (3.3 g) in pyridine (80 ml) was heated at 150°C for 12 h in an autoclave, then concentrated. The residue was chromatographed on a column of alumina

with AcOEt–petr. ether (1: 15) to give 1.8 g (59%) of **1f** as a viscous oil, which was identical with the authentic sample prepared by method a.

Reaction of 2 with *tert*-Butyl Bromide——*tert*-Butyl bromide (10 g) was added to a mixture of **2** (5 g), K_2CO_3 (10 g), and dry DMF (100 ml) with cooling. The mixture was heated at 60°C for 12 h, poured into ice-water, and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried, and concentrated. The residue was chromatographed on a column of alumina. Elution with cyclohexane gave 0.32 g (5%) of 2-(*tert*-butylthio)benzoxazole[7] (**3b**). Further elution with benzene gave 1.32 g (19%) of 3-*tert*-butylbenzoxazoline-2-thione (**1b**), mp 129—132°C (from cyclohexane). *Anal.* Calcd for $C_{11}H_{13}NOS$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.91; H, 6.49; N, 6.80. NMR ($CDCl_3$) δ: 2.04 (9H, s, $CH_3\times3$), 7.08—7.87 (4H, m, aromatic H). MS *m/e*: 207 (M^+).

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