A Convenient Synthesis of 2-Sulfanylbenzoselenazole Derivatives *via* the Reaction of 2-Lithiophenyl Isothiocyanates with Selenium

by **Kazuhiro Kobayashi***[a]) and **Yuki Yokoi**[a])

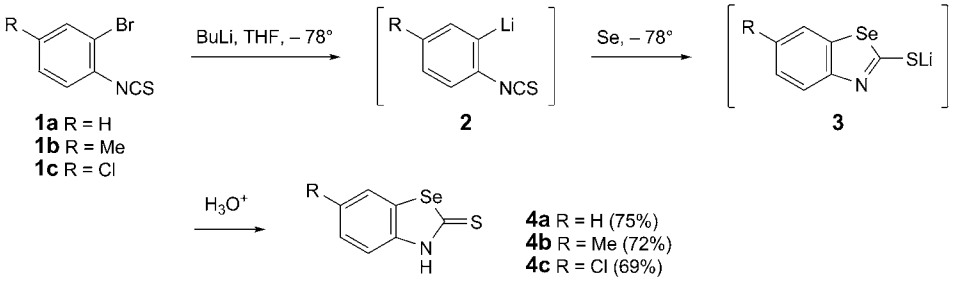
[a]) Division of Applied Chemistry, Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-minami, Tottori 680-8552, Japan (phone/fax: +81-857-315263; e-mail: kkoba@chem.tottori-u.ac.jp)

The title compounds have been prepared from 2-bromophenyl isothiocyanates **1**. Thus, 2-lithiophenyl isothiocyanates **2**, obtained from **1** and BuLi through Br/Li exchange, reacted with Se at −78° to form lithium benzoselenazole-2-thiolates **3**, which, upon aqueous workup, afforded benzoselenazole-2(3*H*)-thiones **4**. The thiolates **3** were alkylated with reactive alkyl halides and acylated with carboxylic acid chlorides to give 2-(alkylsulfanyl)benzoselenazoles **5** and *S*-(benzoselenazol-2-yl) thiocarboxylates **6**, respectively.

Introduction. – Some compounds with the benzoselenazole skeleton have been reported to exhibit biological activities [1], and some general procedures are available for the preparation of benzoselenazoles [1][2]. For example, *Fujiwara et al.* have reported an efficient method based on Cu-catalyzed cyclization of the adducts derived from the addition reactions of 2-halophenyl isoselenocyanates with amines, alcohols, and thiols [2a]. The preparation of *N*-substituted benzoselenazol-2-amines by Cu-catalyzed addition–cyclization of 2-iodobenzenamines with isoselenocyanates has been reported by *Sashida* and co-workers [2b]. On the other hand, we have recently reported that 2-lithiophenyl isothiocyanates, generated from 2-bromophenyl isothiocyanates and BuLi through Br/Li exchange, react with electrophiles, such as aldehydes, ketones, butenolide, or isothiocyanates, to give 1,4-dihydro-3,1-benzoxazine-2-thiones [3] or benzoquinazoline-2,4(1*H*,3*H*)-dithiones [4]. As part of our continuing study on the synthesis of benzo-fused heterocycles utilizing 2-lithiophenyl isothiocyanates, we, therefore, investigated the possibility of the preparation of 2-sulfanylbenzoselenazole derivatives *via* the reaction of these Li compounds with Se. Here, we report the results of our investigation, which offer an efficient preparation of benzoselenazole-2(3*H*)-thiones **4**, 2-(alkylsulfanyl)benzoselenazoles **5**, and *S*-(benzoselenazol-2-yl) thiocarboxylates **6**. To the best of our knowledge, this is the first report for the preparation of benzoselenazoles of type **6**.

Results and Discussion. – First, the synthesis of benzoselenazole-2(3*H*)-thiones **4** was conducted as illustrated in *Scheme 1*. 2-Bromophenyl isothiocyanates **1** were treated with BuLi in THF at −78° to generate 2-lithiophenyl isothiocyanates **2**, which were then allowed to react with Se. Attack of these carbanions on Se and the subsequent ring closure of the resulting 2-isothiocyanatobenzeneselenide by the intramolecular addition of selenide to the isocyanate C-atom proceeded rapidly at this

Scheme 1



temperature to lead to the formation of lithium benzoselenazole-2-thiolate intermediates **3**, which were protonated by acidic aqueous workup to give **4** in relatively good yields.

The preparation of 2-(alkylsulfanyl)benzoselenazoles **5** was then accomplished outlined as in *Scheme 2*. The intermediates **3**, generated as described above, were treated with alkyl halides, and the temperature was raised to room temperature. The *S*-alkylation could be achieved only using reactive alkyl halides compiled in the *Table*. However, the yields of **5** were relatively good as can be seen from this *Table*. Butylsulfanyl derivatives, which might be expected from the *S*-alkylation of **3** with 1-bromobutane, could not be detected. It is *natural* that EtBr did not react under these reaction conditions.

Scheme 2

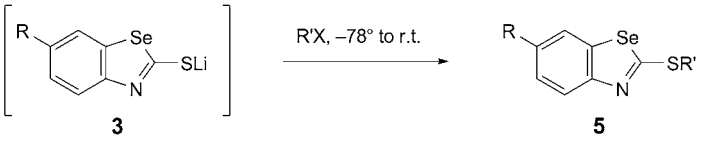


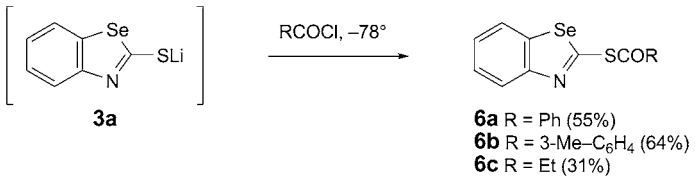
Table. *Preparation of 2-Sulfanyl-benzoselenazoles* **5**

Entry	**1**	R′X	**5**	Yield[a]) [%]
1	**1a** (R = H)	MeI	**5a**	68
2	**1a**	EtI	**5b**	64
3	**1a**	CH_2=$CHCH_2$Br	**5c**	74
4	**1a**	BnBr	**5d**	69
5	**1b** (R = Me)	CH_2=$CHCH_2$Br	**5e**	68
6	**1c** (R = Cl)	MeI	**5f**	68

[a]) Yields of isolated products.

Subsequently, *S*-(benzoselenazol-2-yl) thiocarboxylates **6** were obtained as shown in *Scheme 3*. When carboxylic acid chlorides were reacted with intermediate **3a**, *S*-acylation proceeded rapidly even at $-78°$ to afford the desired products **6** in moderate-to-fair yields.

Scheme 3



3a

6a R = Ph (55%)
6b R = 3-Me–C_6H_4 (64%)
6c R = Et (31%)

In conclusion, we have demonstrated that the reactions of 2-lithiophenyl isothiocyanates with Se allow convenient syntheses of benzoselenazole-2(3*H*)-thiones, 2-(alkylsulfanyl)benzoselenazoles, and *S*-(benzoselenazol-2-yl) thiocarboxylates. The ready availability of the starting materials coupled with the ease of operations render the presented procedures attractive.

Experimental Part

General. All of the org. solvents used were dried on 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: *Perkin–Elmer Spectrum65* FT-IR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *JEOL ECP 500 FT* and *JEOL LA400FT* NMR spectrometers, at 500 and 400 MHz, resp.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. ^{13}C-NMR: *JEOL ECP 500 FT* and *JEOL LA400FT* NMR spectrometers, at 125 and 100 MHz, resp.; δ in ppm rel. to Me_4Si as internal standard. LR-EI-MS (70 eV): *JEOL JMS AX 505 HA* spectrometer; in *m*/*z*.

2-Bromo-4-chloro-1-isothiocyanatobenzene (**1c**) was prepared by the procedure reported previously by us [3]. BuLi was supplied by *Asia Lithium Corporation*. All other chemicals used in this study were commercially available; **1a** from *Tokyo Chemical Industry Co., Ltd.*, and **1b** from *Wako Pure Chemical Industries, Ltd.*.

*Benzoselenazole-2(3*H*)-thione* (**4a**) [5][6]. *General Procedure.* To a stirred soln. of **1a** (0.21 g, 1.0 mmol) in THF (4 ml) at $-78°$ was added dropwise BuLi (1.6M in hexane; 1.0 mmol). After 5 min, Se (79 mg, 1.0 mmol) was added, and stirring was continued for an additional 30 min at the same temp. Aq. sat. NH_4Cl (10 ml) was added, and the mixture was warmed to r.t. and extracted with AcOEt (3×10 ml). The combined extracts were washed with brine (10 ml), dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2) to give **4a** (0.15 g, 75%). White solid. R_f (AcOEt/hexane 1:5) 0.60. M.p. 155–157° (hexane/Et_2O) ([6]: 157°). IR (KBr): 3105, 1500, 1426, 1316, 1006. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.24 (*ddd*, *J* = 8.0, 7.4, 1.1, 1 H); 7.30 (*d*, *J* = 8.0, 1 H); 7.35 (*td*, *J* = 7.4, 1.1, 1 H); 7.51 (*d*, *J* = 7.4, 1 H); 10.99 (br. *s*, 1 NH).

*6-Methylbenzoselenazole-2(3*H*)-thione* (**4b**). White solid. M.p. 164–167° (hexane/$CHCl_3$). IR (KBr): 3102, 1497, 1478, 1319, 1025. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.39 (*s*, 3 H); 7.15 (*d*, *J* = 8.4, 1 H); 7.18 (*d*, *J* = 8.4, 1 H); 7.35 (*s*, 1 H); 10.85 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.14; 113.07; 124.98; 128.16; 130.38; 135.04; 139.34; 193.32. MS: 229 (100, M^+). Anal. calc. for C_8H_7NSSe (228.95): C 42.11, H 2.35, N 6.54; found: C 42.08, H 2.38, N 6.44.

*6-Chlorobenzoselenazole-2(3*H*)-thione* (**4c**). White solid. M.p. 230–233° (hexane/CH_2Cl_2). IR (KBr): 3100, 1489, 1458, 1313, 1025. ^{1}H-NMR (500 MHz, (D_6)DMSO): 7.27 (*d*, *J* = 9.2, 1 H); 7.41 (*dd*, *J* = 9.2, 1.6, 1 H); 7.87 (*d*, *J* = 1.6, 1 H); 13.69 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 114.60; 125.14; 127.24; 128.66; 131.55; 141.70; 194.18. MS: 249 (100, M^+). Anal. calc. for $C_7H_4ClNSSe$ (248.59): C 33.82, H 1.62, N 5.63; found: C 33.74, H 1.69, N 5.50.

2-(Methylsulfanyl)benzoselenazole (**5a**) [7]. *General Procedure.* Compound **1a** (0.21 g, 1.0 mmol) in THF (4 ml) was treated with BuLi (1.0 mmol) and Se (79 mg, 1.0 mmol) as described for the preparation

of **4**. After 30 min, MeI (0.14 g, 1.0 mmol) was added, and then the temp. was raised to r.t. over 30 min. The resulting mixture was worked up as described for the preparation of **4**, and the residue was purified by CC (SiO_2) to give **5a** (0.13 g, 58%). Yellow oil. R_f (AcOEt/hexane 1:20) 0.36. IR (neat): 1610, 1473, 1434. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.78 (*s*, 3 H); 7.23 (*ddd*, *J* = 7.8, 7.3, 1.0, 1 H); 7.41 (*ddd*, *J* = 8.3, 7.4, 1.0, 1 H); 7.79 (*d*, *J* = 7.8, 1 H); 7.89 (*d*, *J* = 8.3, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 16.74; 122.78; 124.15; 124.24; 126.17; 137.98; 154.78; 169.70.

2-(Ethylsulfanyl)benzoselenazole (**5b**). Yellow oil. R_f (AcOEt/hexane 1:20) 0.54. IR (neat): 1624, 1474, 1436. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.49 (*t*, *J* = 7.3, 3 H); 3.34 (*q*, *J* = 7.3, 2 H); 7.21 (*ddd*, *J* = 7.8, 7.3, 1.0, 1 H); 7.40 (*ddd*, *J* = 7.8, 7.3, 1.0, 1 H); 7.78 (*d*, *J* = 7.8, 1 H); 7.88 (*d*, *J* = 7.8, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.44; 28.61; 122.83; 124.17; 124.23; 126.10; 138.02; 154.75; 168.63. MS: 243 (100, M^+). Anal. calc. for C_9H_9NSSe (242.20): C 44.63, H 3.75, N 5.78; found: C 44.72, H 3.70, N 5.71.

2-[(Prop-2-en-1-yl)sulfanyl]benzoselenazole (**5c**). Yellow oil. R_f (AcOEt/hexane 1:5) 0.41. IR (neat): 1634, 1473, 1450. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.99 (*dt*, *J* = 6.9, 1.1, 2 H); 5.22 (*dd*, *J* = 10.3, 1.1, 1 H); 5.40 (*dd*, *J* = 13.2, 1.1, 1 H); 5.99–6.08 (*m*, 1 H); 7.22 (*ddd*, *J* = 8.0, 7.4, 1.1, 1 H); 7.40 (*ddd*, *J* = 8.0, 7.4, 1.1, 1 H); 7.78 (*dd*, *J* = 8.0, 1.1, 1 H); 7.88 (*dd*, *J* = 8.0, 1.1, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 36.76; 119.20; 122.96; 124.25; 124.32; 126.13; 132.28; 138.24; 154.55; 167.64. MS: 255 (100, M^+). Anal. calc. for $C_{10}H_9NSSe$ (254.21): C 47.25, H 3.57, N 5.51; found: C 47.08, H 3.66, N 5.38.

2-[(Phenylmethyl)sulfanyl]benzoselenazole (**5d**). Yellow oil. R_f (AcOEt/hexane 1:10) 0.61. IR (neat): 1625, 1471, 1434. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.59 (*s*, 2 H); 7.22 (*dd*, *J* = 8.0, 7.4, 1 H); 7.28 (*dd*, *J* = 8.0, 7.4, 1 H); 7.33 (*t*, *J* = 7.4, 2 H); 7.41 (*t*, *J* = 7.4, 1 H); 7.46 (*d*, *J* = 7.4, 2 H); 7.78 (*d*, *J* = 8.0, 1 H); 7.91 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 38.14; 122.94; 124.29; 124.34; 126.15; 127.72; 128.69; 129.16; 136.12; 138.28; 154.50; 167.79. MS: 305 (100, M^+). Anal. calc. for $C_{14}H_{11}NSSe$ (304.27): C 55.26, H 3.64, N 4.60; found: C 55.21, H 3.69, N 4.37.

5-Methyl-2-[(prop-2-en-1-yl)sulfanyl]benzoselenazole (**5e**). Yellow oil. R_f (AcOEt/hexane 1:5) 0.59. IR (neat): 1634, 1479, 1453. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.42 (*s*, 3 H); 3.97 (*d*, *J* = 6.9, 2 H); 5.21 (*d*, *J* = 9.9, 1 H); 5.39 (*d*, *J* = 17.6, 1 H); 5.99–6.07 (*m*, 1 H); 7.20 (d, *J* = 8.4, 1 H); 7.58 (*s*, 1 H); 7.76 (*d*, *J* = 8.4, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 21.26; 36.80; 119.12; 122.42; 124.23; 127.45; 132.36; 134.42; 138.36; 152.60; 166.19. MS: 269 (100, M^+). Anal. calc. for $C_{11}H_{11}NSSe$ (268.24): C 49.25, H 4.13, N 5.22; found: C 49.07, H 4.15, N 5.13.

5-Chloro-2-(methylsulfanyl)benzoselenazole (**5f**). Pale-yellow solid. M.p. 81–83° (hexane/Et_2O). IR (KBr): 1628, 1477, 1444. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.78 (*s*, 3 H); 7.36 (*dd*, *J* = 8.8, 2.0, 1 H); 7.76 (*d*, *J* = 2.0, 1 H); 7.77 (*d*, *J* = 8.8, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 16.72; 123.22; 123.86; 126.76; 129.88; 139.05; 153.36; 170.16. MS: 263 (100, M^+). Anal. calc. for $C_8H_6ClNSSe$ (262.62): C 36.59, H 2.30, N 5.33; found: C 36.46, H 2.41, N 5.29.

S-(*Benzoselenazol-2-yl) Thiobenzoate* (**6a**). *General Procedure.* Compound **1a** (0.21 g, 1.0 mmol) in THF (4 ml) was treated with BuLi (1.0 mmol) and Se (79 mg, 1.0 mmol) in as described for the preparation of **4**. After 30 min, BzCl (0.14 g, 1.0 mmol) was added, and stirring was continued for an additional 5 min. The resulting mixture was worked up as described for the preparation of **4**, and the residue was purified by CC (SiO_2; AcOEt/hexane 1:10) to give **6a** (0.18 g, 55%). Yellow solid. M.p. 120–123° (Et_2O/THF). IR (KBr): 1658, 1620, 1480, 1426. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37 (*ddd*, *J* = 7.8, 7.3, 1.0, 1 H); 7.50 (*ddd*, *J* = 7.8, 7.3, 1.0, 1 H); 7.57 (*t*, *J* = 7.3, 2 H); 7.70 (*tt*, *J* = 7.3, 1.4, 1 H); 8.00 (*dd*, *J* = 7.8, 1.0, 1 H); 8.06 (*dd*, *J* = 7.8, 1.0, 1 H); 8.08 (*dd*, *J* = 7.3, 1.4, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 123.63; 125.19; 126.59; 127.51; 129.02; 129.65; 129.72; 134.76; 135.48; 149.74; 160.67; 187.32. MS: 319 (8.6, M^+), 105 (100). Anal. calc. for $C_{14}H_9NOSSe$ (318.25): C 52.84, H 2.85, N 4.40; found: C 52.60, H 2.95, N 4.34.

S-(*Benzoselenazol-2-yl) 3-Methylthiobenzoate* (**6b**). Pale-yellow solid. M.p. 111–113° (hexane/$CHCl_3$). IR (KBr): 1657, 1602, 1480, 1422. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.47 (*s*, 3 H); 7.37 (*ddd*, *J* = 7.8, 7.3, 1.0, 1 H); 7.42–7.51 (*m*, 3 H); 7.87–7.88 (*m*, 2 H); 8.00 (*d*, *J* = 7.8, 1 H); 8.06 (*d*, *J* = 7.8, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.35; 124.01; 124.10; 124.86; 125.21; 126.31; 128.01; 129.04; 135.57; 135.59; 136.94; 139.23; 152.01; 160.88; 187.62. MS: 333 (8.5, M^+), 119 (100). Anal. calc. for $C_{15}H_{11}NOSSe$ (332.28): C 54.22, H 3.34, N 4.22; found: C 54.06, H 3.62, N 4.16.

S-(*Benzoselenazol-2-yl) Thiopropanoate* (**6c**). White solid. M.p. 52–56° (hexane/Et_2O). IR (KBr): 1702, 1460, 1429. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.33 (*t*, *J* = 7.4, 3 H); 2.86 (*q*, *J* = 7.4, 2 H); 7.34 (*dd*, *J* = 8.0, 7.4, 1 H); 7.47 (*dd*, *J* = 8.0, 7.4, 1 H); 7.96 (*d*, *J* = 8.0, 1 H); 8.02 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR (100 MHz,

$CDCl_3$): 9.25; 37.71; 123.99; 124.07; 125.27; 126.28; 136.97; 151.77; 160.29; 195.76. MS: 270 (3.1, M^+), 213 (100). Anal. calc. for $C_{10}H_9NOSSe$ (270.21): C 44.45, H 3.36, N 4.22; found: C 44.46, H 3.27, N 4.11.

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REFERENCES

[1] K. Shimada, *Sci. Synth., Knowledge Updates* **2010**, 455; C.-K. Ryu, J.-Y. Han, O.-J. Jung, S.-K. Lee, J. Y. Lee, S. H. Jeong, *Bioorg. Med. Chem. Lett*. **2005**, *15*, 679. See also pertinent refs. cit. in these papers.
[2] a) S. Fujiwara, Y. Asanuma, T. Shin-ike, N. Kambe, *J. Org. Chem*. **2007**, *72*, 8087; b) M. Kaname, M. Minoura, H. Sashida, *Tetrahedron Lett*. **2011**, *52*, 505; see also refs. cit. in these papers; W.-D. Pfeifer, *Sci. Synth.* **2002**, *11*, 991.
[3] K. Kobayashi, Y. Yokoi, T. Komatsu, H. Konishi, *Tetrahedron* **2010**, *66*, 9336.
[4] K. Kobayashi, Y. Yokoi, H. Konishi, *Synthesis* **2010**, 1526.
[5] J. R. Bartels-Keith, M. T. Burgess, J. M. Stevenson, *J. Org. Chem*. **1977**, *42*, 3725.
[6] V. Ettel, M. Semonsky, J. Kunak, A. Cerny, *Chem. Listy Vedu Prumysl* **1952**, 46, 756 (*Chem Abstr.* **1953**, *47*, 72773).
[7] S. Hünig, H. Balli, *Liebigs Ann. Chem*. **1957**, *609*, 160.

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