Reactions of 2-Benzoselenopyrylium Salts with Hydrazine: A New Easy Access to 5*H*-2,3-Benzodiazepines[1)]

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While the solvent-free reactions of the 2-benzoselenopyrylium salts (9) with methyl- or phenylhydrazine afforded the 1-hydrazino-1*H*-isoselenochromenes (11, 12), the treatment of the salts (9) with anhydrous hydrazine in dry acetonitrile resulted in a ring transformation to give the 5*H*-2,3-benzodiazepines (13) in one-pot under mild conditions in moderate yields.

Key words 2-benzoselenopyrylium salt; 5*H*-2,3-benzodiazepine; ring transformation; hydrazine

The ring transformation is a potentially useful tool for the construction of various heterocyclic rings. The reactions of pyrylium or thiopyrylium salts, six-membered cationic heteroaromatics containing an oxygen or sulfur atom, with nitrogen-containing nucleophiles to afford a variety of nitrogen-containing heterocyclic compounds provide one of the most effective examples of the ring transformation.[2,3)] Six-membered heterocycles such as pyridines, quinolines, isoquinolines, acridines and pyridine *N*-oxides are obtained by the reactions of the pyrylium salts with ammonia derivatives. The reaction of the pyrylium salts with hydrazine affords the pyridinium betaines.[4)] The thiopyrylium salts are also converted into these heterocycles with less reactivity. In 1974, Snieckus *et al.*[5)] described the preparation of the monocyclic 4*H*-1,2-diazepines by the reaction of 2,4,6-triphenylthiopyrylium salts with hydrazine *via* the ring transformation of the thiopyrylium salts.

While the chemistry of the selenopyrylium salts including the ring transformation has not yet been sufficiently examined, we previously succeeded in the practical and facile preparations[6)] of the 2-benzoselenopyrylium (**1A**)[7)] and 2-benzotelluropyrylium salts (**1B**),[8)] which are selenium- or tellurium-containing six-membered heteroaromatic cation rings. These pyrylium salts (**1**) easily reacted with various nucleophiles[9)] such as the alkoxide ion, amine, Grignard reagent, organocopper reagent,[10)] and an active methylene compound to afford the corresponding 1-substituted 1*H*-isoselenochromenes (**2A**) or isotellurochromenes (**2B**) (Chart 1). More recently, we reported the interconversion of the 1-benzoselenopyrylium salts into the 1,3-benzoselenazepines through thermal ring expansion of the 2-azidoselenochromenes.[11)]

In our knowledge, there are two reports[12,13)] on the syntheses of the 2,3-benzodiazepines, fully unsaturated nitrogen-containing seven-membered heterocycles, as shown in Chart 2. Sharp *et al.*[12)] reported the preparation of 1*H*-2,3-benzodiazepines (**5**) from the tosylhydrazones (**3**) *via* the diazo intermediates (**4**) by thermal intramolecular cyclization in 1973. The 5*H*-2,3-benzodiazepines (**8**)[13)] were obtained by photochemical ring expansion of the isoquinoline *N*-imides (**7**) under basic conditions *via* the presumed tautomerized 1*H* derivatives. In this paper, we report the one-pot ring conversion of the 2-benzoselenopyrylium salts into the 5*H*-2,3-benzodiazepines.

The starting 2-benzoselenopyrylium salts (**9a**—**f**) were prepared by the reported method,[6,9)] while other pyrylium salts (**9g**, **h**) were synthesized from **9f** as shown in Chart 3. The salt (**9f**) was reacted with Grignard reagents to give the 1-substituted isoselenochromenes (**10g**, **h**), which were treated with triphenylcarbenium tetrafluoroborate (Ph_3C^+ BF_4^-) to afford the corresponding selenopyrylium tetrafluoroborates (**9g**, **h**) in good yields.

The reaction of the 3-*tert*-butyl-2-benzoselenopyrylium salt (**9a**) with methylhydrazine under a solvent-free condition at −20 °C resulted in the selective nucleophilic attack at the C-1 position on the heterocyclic cation ring to give 1-methylhydrazino-1*H*-isoselenochromene (**11**) in very high yield as the sole product in analogy with the amines as described in a previous paper.[9)] Phenylhydrazine also reacted with the salt (**9a**) to afford the 1-phenylhydrazinoisochromene (**12**). In contrast, when the 2-benzoselenopyrylium salt (**9a**) was treated with anhydrous hydrazine, the transformation reaction of the selenium-containing six-membered ring skeleton into the 5*H*-2,3-benzodiazepine (**13a**) occurred accompany-

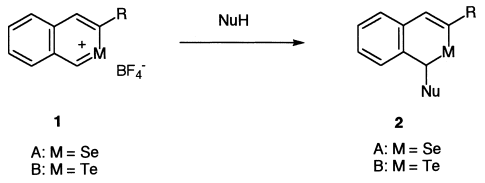

Chart 1

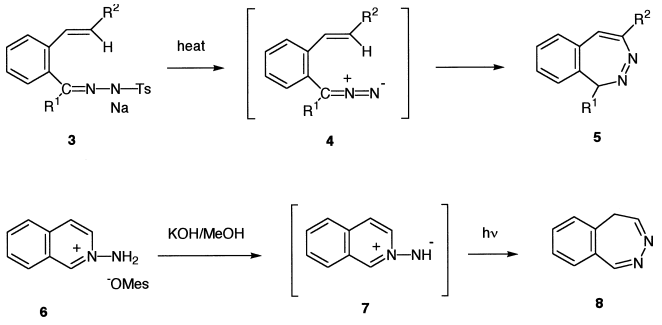

Chart 2

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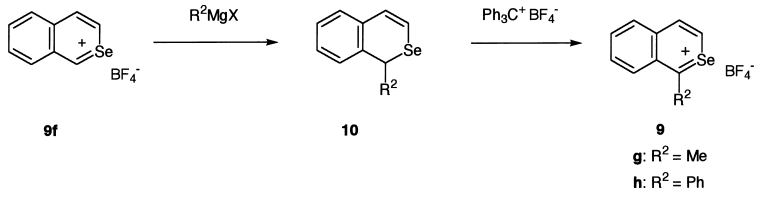

Chart 3

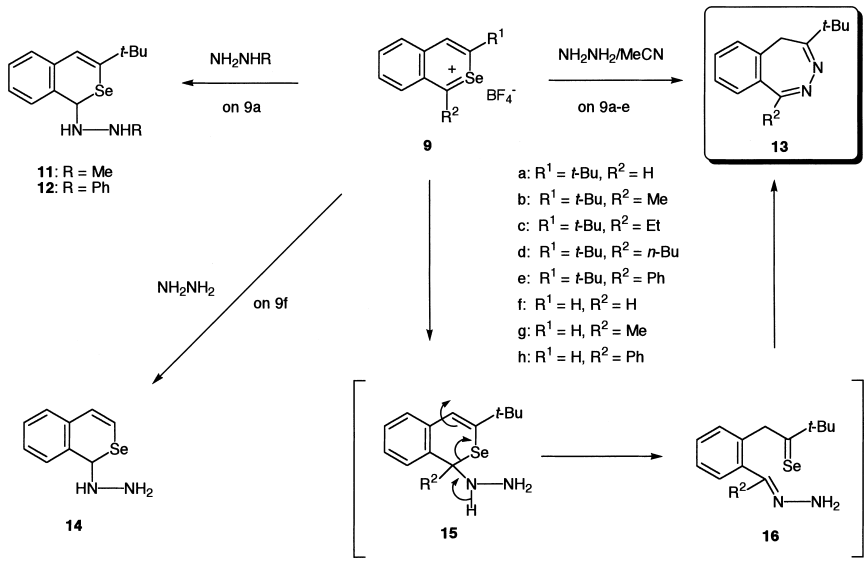

Chart 4

ing with selenium element extrusion. We examined the optimum to increase the yields of this ring transformation. It turned out that the treatment of the salt (**9a**) with a large excess of anhydrous hydrazine in dry acetonitrile at room temperature overnight gave the diazepine (**13a**) in 47% yield as the sole characterized product. The shortening of the reaction time and use of other polar solvents such as dichloromethane and tetrahydrofuran failed to give any improved results. 1-Alkyl and 1-phenyl substituted 3-*tert*-butyl-5*H*-2,3-benzodiazepines (**13b**—**e**) were also produced from the corresponding 2-benzoselenopyrylium salts (**9b**—**e**) in moderate yields. However, the unsubstituted (**9f**) and 1-substituted selenopyrylium salts (**9g**, **h**) did not react with hydrazine to afford the corresponding diazepines (**13f**—**h**) under the same conditions. The reaction of **9f** with hydrazine under the solvent free conditions gave 1-hydrazino-1*H*-isoselenochromene (**14**) in 76% yield. A complex mixture was obtained from the 1-substituted selenopyrylium salts (**9g**, **h**). These results are summarized in Table 1. The structures of the obtained 2,3-benzodiazepines (**13a**—**e**) were characterized by spectral comparison with those of the reported diazepines.[13] The unsubstituted diazepine was found to decompose by chromatography on silica gel or alumina, however, the 4-*tert*-butyl derivatives (**13a**—**e**) could be purified by silica gel chromatography.

The formation of the 5*H*-2,3-benzodiazepines (**13**) from the selenopyrylium salts (**9**) may proceed by nucleophilic attack of the hydrazine to generate the 1-hydrazino-1*H*-isoselenochromenes (**15**) followed by ring opening into the selenoketone intermediates (**16**), which would recyclize to the stable products (**13**) as shown in Chart 4. The difference

Table 1. 5*H*-2,3-Benzodiazepines (**13**)

Compd. No.	R^1	R^2	Yield (%)	Appearance, mp/°C
13a	*t*-Bu	H	47	Pale yellow prisms, mp 99
13b	*t*-Bu	Me	41	Colorless prisms, mp 110—112
13c	*t*-Bu	Et	31	Pale yellow prisms, mp 96—97
13d	*t*-Bu	*n*-Bu	35	Pale yellow prisms, mp 71—73
13e	*t*-Bu	Ph	57	Pale yellow prisms, mp 148—149

in the reactivity of the 3-*tert*-butyl-2-benzoselenopyrylium salts (**9a**—**e**) and the other pyrylium salts (**9f**—**h**) having no *tert*-butyl group with hydrazine could be explained by the following theories. In general, selenocarbonyl compounds (selenoaldehydes and selenoketones) are unstable.[14,15] However, selenoketones which the introduction of a bulky group on the selenocalbonyl α-carbons stabilizes could even be isolated.[16] The selenoketones (**16a**—**e**) generated from the pyrylium salts (**9a**—**e**) are kinetically stabilized by the steric protection of the *tert*-butyl group on the α-position. Thus, the reaction of the 3-*tert*-butylpyrylium salts (**9a**—**e**) with hydrazine favors the reaction of the anticipated 2,3-benzodiazepines (**13a**—**e**) *via* the selenoketone intermediates (**16a**—**e**). On the other hand, the selenoaldehydes (**16f**—**h**) from **9f**—**h** are quite unstable. This reaction could not proceed through these intermediates (**16f**—**h**); the isoselenochromene (**14**) was obtained as the sole product. The tellurium analogue, the 2-benzotelluropyrylium salts, reacted with anhydrous hydrazine under the same conditions to afford no benzodiazepines; the starting materials decomposed. The corre-

sponding intermediates, the telluroketones, would be more unstable because of the decrease in the Te=C π bond energy.[17—20]

In conclusion, the facile one-pot alternative preparation of the 5*H*-2,3-benzodiazepines from the 2-benzoselenopyrylium salts was achieved in the present study.

Experimental

Melting points were measured on a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were determined with a Horiba FT-720 spectrometer. Mass spectra (MS) and HR-MS were recorded on a JEOL JMS-DX300 instrument. NMR spectra were determined with a JEOL EX-90A (90 MHz) or a JEOL JNM-GSX 400 (400 MHz) spectrometer in $CDCl_3$ or CD_3CN using tetramethylsilane as internal standard and *J* values are given in Hz. Microanalyses were performed in the Microanalytical Laboratory in this Faculty.

Starting Pyrylium Salts 2-Benzoselenopyrylium salts (**9a**—**f**) were prepared by the reported methods.[9] 1-Methyl (**9g**) and 1-phenyl-2-benzoselenopyrylium salts (**9h**) were prepared from **9f** according to the literature.[9]

1-Methyl-1*H*-isoselenochromene (10g) MeMgI (15 mmol) in ether solution was slowly added to a suspended mixture of the pyrylium salt (**9f**, 10 mmol) in ether (100 ml) at 0 °C under an argon atmosphere. The resulting mixture was stirred under the conditions for 30 min, and quenched by the addition of saturated aqueous NH_4Cl solution (50 ml). The resulting mixture was extracted with Et_2O (100 ml×3). The organic layer was washed with brine (100 ml×2), dried ($MgSO_4$) and evaporated *in vacuo*. The resulting residue was purified by silica gel chromatography (hexane–CH_2Cl_2=10 : 1) to give **10g** (24%), yellow oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.64 (3H, d, *J*=7.1 Hz, 1-Me), 4.00 (1H, dq, *J*=1.3, 7.1 Hz, 1-H), 6.73 (1H, dd, *J*=1.3, 9.7 Hz, 3-H), 6.95 (1H, d, *J*=9.7 Hz, 4-H), 7.0—7.3 (4H, m, Ph–H). EI-MS *m/z* (relative intensity): 210 (M^+, 80), 195 (100), 115 (70). EI-HR-MS *m/z*: 209.9950 (Calcd for $C_{10}H_{10}Se$: 209.9948).

1-Phenyl-1*H*-isoselenochromene (10h) The pyrylium salt (**9f**) was treated with PhMgBr instead of MeMgI and worked up as described for the preparation of **9g** to give **10h** (20%), pale yellow oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 5.28 (1H, s, 1-H), 6.72 (1H, d, *J*=9.7 Hz, 3-H), 7.02 (1H, d, *J*=9.7 Hz, 4-H), 6.9—7.3 (9H, m, Ph–H). EI-MS *m/z* (relative intensity): 272 (M^+, 55), 191 (100). EI-HR-MS *m/z*: 272.0099 (Calcd for $C_{15}H_{12}Se$: 272.0105).

1-Methyl-2-benzoselenopyrylium Tetrafluoroborate (9g) Ph_3C^+ BF_4^- (727 mg, 2.2 mmol) was added to a stirred solution of the isochromene (**10g**, 2.0 mmol) in dry $MeNO_2$ (4 ml) and the mixture was stirred at room temperature for 2 h. To the reaction mixture was added dry Et_2O (40 ml) to precipitate **9g** (92%), pale green prisms, mp 77—80 °C (from $CHCl_3$). IR (KBr) ν 1070 cm^{-1} (BF_4^-). ^{1}H-NMR (90 MHz, CD_3CN) δ: 3.56 (3H, s, 1-Me), 8.1—8.8 (4H, m, Ph–H), 9.00 (1H, d, *J*=9.7 Hz, 4-H), 9.59 (1H, d, *J*=9.7 Hz, 3-H). *Anal.* Calcd for $C_{10}H_9BF_4Se$: C, 40.72; H, 3.08. Found: C, 40.60; H, 2.88.

1-Phenyl-2-benzoselenopyrylium Tetrafluoroborate (9h) The isochromene (**10h**) was treated with Ph_3C^+ BF_4^- and worked up as described for the preparation of **9g** to give **9h** (76%), yellow prisms, 177—180 °C (from $CHCl_3$). IR (KBr) ν 1083 cm^{-1} (BF_4^-). ^{1}H-NMR (90 MHz, CD_3CN) δ: 7.7—7.9 and 8.1—8.6 (9H, m, Ph–H), 9.11 (1H, d, *J*=9.7 Hz, 4-H), 9.79 (1H, d, *J*=9.7 Hz, 3-H). *Anal.* Calcd for $C_{15}H_{11}BF_4Se$: C, 50.46; H, 3.11. Found: C, 50.33; H, 3.01.

3-*tert*-Butyl-1-(2-methylhydrazino)-1*H*-isoselenochromene (11) The pyrylium salt (**9a**, 0.3 mmol) was dissolved in methyhydrazine (1.5 ml) at −70 °C under an argon atmosphere. The reaction mixture was allowed to warm to 0 °C with stirring overnight, and extracted with benzene (20 ml×3). The organic layer was washed with brine (30 ml×2), dried over ($MgSO_4$), and evaporated. Product was obtained in a nearly pure form in almost quantitative yield, and decomposed during the attempted purification by silica gel chromatography. Yield 96%, yellow oil. IR (neat) ν 3330 cm^{-1} (NH). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.35 (9H, s, *t*-Bu), 2.20 (3H, s, NMe), 3.0 (2H, br, NH–NH–), 5.63 (1H, s, 1-H), 6.70 (1H, s, 4-H), 7.1—7.4 (4H, m, Ph–H). EI-MS *m/z* (relative intensity): 294 (M^+-2, 3), 251 (100). EI-HR-MS *m/z*: 294.0641 (M^+-H_2, Calcd for $C_{14}H_{18}N_2Se$: 294.0636).

3-*tert*-Butyl-1-(2-phenylhydrazino)-1*H*-isoselenochromene (12) The mixture of the pyrylium salt (**9a**, 0.3 mmol) and phenylhydrazine (1.25 ml) was stirrred at room temperature under an argon atmosphere overnight, and worked up as described for the preparation of **11** to give **12**. Yield 99%, yellow oil. IR (neat) ν 3319 cm^{-1} (NH). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.33 (9H, s, *t*-Bu), 3.4—3.6 (2H, br, NH–NH–), 6.13 (1H, s, 1-H), 6.89 (1H, s, 4-H), 6.7—7.5 (9H, m, Ph–H). EI-MS *m/z* (relative intensity): 356 (M^+-2, 45), 251 (100). EI-HR-MS *m/z*: 356.0784 (M^+-H_2, Calcd for $C_{19}H_{20}N_2Se$: 356.0793).

Treatment of 2-Benzoselenopyrylium Salts (9) with Hydrazine To a solution of selenopyrylium salt (**9**, 0.3 mmol) in acetonitrile (5 ml) was added anhydrous hydrazine (1.25 ml, 26 mmol) all at one portion at room temperature. The reaction mixture was stirred under the same conditions overnight, and poured into ice-water. The aqueous mixture was extracted with benzene (20 ml×3). The organic layer was washed with brine (30 ml×2), dried ($MgSO_4$), and evaporated. The resulting residue was purified by silica gel chromatography (CH_2Cl_2–acetone=10 : 1) to give 5*H*-2,3-benzodiazepines (**13**).

4-*tert*-Butyl-5*H*-2,3-benzodiazepine (**13a**): ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.21 (9H, s, *t*-Bu), 2.73 and 3.70 (each 1H, d, *J*=12.8 Hz, 5-H_2), 7.1—7.6 (4H, m, Ph–H), 8.57 (1H, s, 1-H). EI-MS *m/z* (relative intensity): 200 (M^+, 40), 185 (55), 158 (100), 117 (41). EI-HR-MS *m/z*: 200.1315 (Calcd for $C_{13}H_{16}N_2$: 200.1313).

4-*tert*-Butyl-1-methyl-5*H*-2,3-benzodiazepine (**13b**): ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.17 (9H, s, *t*-Bu), 2.51 (3H, s, 1-Me), 2.79 and 3.60 (each 1H, d, *J*=12.6 Hz, 5-H_2), 7.2—7.6 (4H, m, Ph–H). EI-MS *m/z* (relative intensity): 214 (M^+, 35), 199 (41), 172 (100), 130 (41). EI-HR-MS *m/z*: 214.1469 (Calcd for $C_{14}H_{18}N_2$: 214.1470).

4-*tert*-Butyl-1-ethyl-5*H*-2,3-benzodiazepine (**13c**): ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.17 (9H, s, *t*-Bu), 1.20 and 2.84 (3H, t, *J*=7.3 Hz, 2H, q, *J*=7.3 Hz, 1-Et), 2.79 and 3.58 (each 1H, d, *J*=12.6 Hz, 5-H_2), 7.15—7.62 (4H, m, Ph–H). EI-MS *m/z* (relative intensity): 228 (M^+, 48), 213 (39), 186 (100), 117 (44). EI-HR-MS *m/z*: 228.1624 (Calcd for $C_{15}H_{20}N_2$: 228.1626).

1-*n*-Butyl-4-*tert*-butyl-5*H*-2,3-benzodiazepine (**13d**): ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.89, 1.20—1.60 and 2.86 (3H, t, *J*=6.2 Hz, 4H, m, 2H, t, *J*=8.2 Hz, 1-*n*-Bu), 1.17 (9H, s, *t*-Bu), 2.78 and 3.59 (each 1H, d, *J*=12.8 Hz, 5-H_2), 7.2—7.6 (4H, m, Ph–H). EI-MS *m/z* (relative intensity): 256 (M^+, 11), 227 (10), 214 (100), 199 (15). EI-HR-MS *m/z*: 256.1942 (Calcd for $C_{17}H_{24}N_2$: 256.1939).

4-*tert*-Butyl-1-phenyl-5*H*-2,3-benzodiazepine (**13e**): ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.22 (9H, s, *t*-Bu), 2.91 and 3.71 (each 1H, d, *J*=12.6 Hz, 5-H_2), 7.2—7.5 and 7.6—7.8 (9H, m, Ph–H). EI-MS *m/z* (relative intensity): 276 (M^+, 35), 261 (25), 234 (100), 193 (53). EI-HR-MS *m/z*: 276.1628 (Calcd for $C_{19}H_{20}N_2$: 276.1626).

1-Hydrazino-1*H*-isoselenochromene (14) This compound was obtained in a nearly pure state and decomposed during the attempted purification with silica gel chromatography. Yield 76%, yellow prisms, mp 82—86 °C (from CH_2Cl_2–hexane). IR (KBr) ν 3284 cm^{-1} (NH). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.24 (3H, br, $NHNH_2$), 5.17 (1H, d, *J*=1.8 Hz, 1-H), 6.68 (1H, dd, *J*=1.8, 9.7 Hz, 3-H), 7.1—7.4 (4H, m, Ph–H), 7.10 (1H, d, *J*=9.7 Hz, 4-H). EI-MS *m/z* (relative intensity): 226 (M^+, 2), 195 (100), 115 (55). EI-HR-MS *m/z*: 226.0015 (Calcd for $C_9H_{10}N_2Se$: 226.0009).

References and Notes

1) This paper constitutes Part 24 in the series "Studies on Tellurium-Containing Heterocycles" Part 23: ref. 11.
2) Doddi G., Ercolani G., "Advances in Heterocyclic Chemistry," Vol. 60, ed. by Katrizky A. R., Academic Press, London, 1994, pp. 65—195.
3) Sugimoto T., *J. Syn. Org. Chem. Jpn.*, **39**, 1—13 (1981).
4) Schneider W., Seebach F., *Chem. Ber.*, **54**, 2285—2298 (1921).
5) Harsis D. J., Kan G. Y.-P., Snieckus V., Klingsberg E., *Can. J. Chem.*, **52**, 2798—2804 (1974).
6) Sashida H., Ohyanagi K., Minoura M., Akiba K.-Y., *J. Chem. Soc., Perkin Trans. 1*, **2002**, 606—612 (2002).
7) Sashida H., Ohyanagi K., *Heterocycles*, **51**, 17—20 (1999).
8) Sashida H., Ohyanagi K., *J. Chem. Soc., Perkin Trans. 1*, **1998**, 2123—2124 (1998).
9) Sashida H., Ohyanagi K., *Chem. Pharm. Bull.*, **52**, 57—62 (2004).
10) Sashida H., Satoh H., Ohyanagi K., *Heterocycles*, **63**, 309—317 (2004).
11) Sashida H., Minamida H., *Chem. Pharm. Bull.*, **52**, 485—487 (2004).
12) Reid A. A., Sharp J. T., Sood H. R., Thorogood P. B., *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2543—2551 (1973).
13) Kurita J., Enkaku M., Tsuchiya T., *Chem. Pherm. Bull.*, **30**, 3764—3769 (1982).
14) Okazaki R., *J. Syn. Org. Chem. Jpn.*, **46**, 1149—1163 (1988).
15) Okuma K., *J. Syn. Org. Chem. Jpn.*, **53**, 218—225 (1995).
16) Back T. G., Barton D. H. R., Britten-Kelly M. R., Guziec F. S., Jr., *Chem. Commun.*, **1975**, 539 (1975).

17) Guziec F. S., Jr., "The Chemistry of Organic Selenium and Tellurium Compounds," Vol. 2, ed. by Patai S., John Wiley & Sons, New York, 1987, pp. 215—273.
18) Segi M., Koyama T., Takata Y., Nakajima T. Suga S., *J. Am. Chem. Soc.*, **111**, 8749—8751 (1989).
19) Erker G., Hoch R., *Angew. Chem. Int. Ed. Engl.*, **28**, 179—180 (1989).
20) Minoura M., Kawashima T., Okazaki R., *J. Am. Chem. Soc.*, **115**, 7019—7020 (1993).