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Synthesis of Selenoxides by Oxidation of Selenides with *t*-Butyl Hypochlorite, and Its Application for Synthesis of Optically Active Selenoxide

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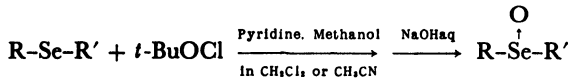
An effective synthesis of selenoxides by the oxidation of selenides with *t*-butyl hypochlorite in the presence of methanol and pyridine followed by hydrolysis is descrived. This oxidation method is particularly effective for the oxidation of selenides which possess electron-withdrawing groups. A synthesis of partially optically active selenoxide with bulky substituents can be achieved using a novel oxidation method.

The oxidation of organic selenides to selenoxides has been carried out using several oxidizing reagents, such as hydrogen peroxide,[1] ozone,[2] peracetic acid,[1] dinitrogen tetraoxide,[3] (dichloroiodo)benzene,[4] *N*-chlorosuccinimide,[5] *t*-butyl hypochlorite[5] and sodium periodate.[4] Among these, sodium periodate is most widely used in laboratories. However, the oxidation of diaryl selenides by this reagent is retarded or completely prevented by the presence of strong electron-withdrawing groups. Ozone is effective in this respect, but its oxidation tends to go beyond the stage of the selenoxides. Nothing is known regarding the oxidation of a selenide substituted with electron-withdrawing groups in the case of oxidation with positive halogenating species. We report here a new synthesis of various selenoxides with an electron-withdrawing substituent through a reaction of selenides and *t*-butyl hypochlorite in the presence of methanol and pyridine followed by hydrolysis.

There had been no example of an optically active selenoxide for a long time. The difficulty of an optical resolution of selenoxide is due to its facile racemization through achiral hydrates.[6] In 1970, optically active selenoxide was isolated for the first time using steroidal systems.[7] Recently, partially optically active selenoxides were synthesized by Davis et al.[8] We also report here on the synthesis of optically active selenoxide using a novel oxidation technique.

Results and Discussion

To a solution of selenide in dichloromethane or acetonitrile were added an equimolar pyridine and an excess amount of methanol. An equimolar *t*-butyl hypochlorite in the same solvent was added slowly



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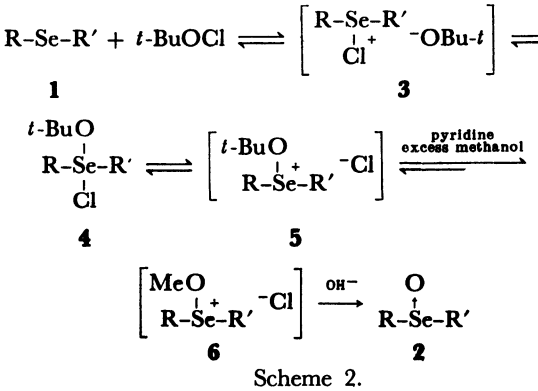
Scheme 1.

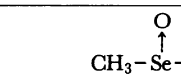
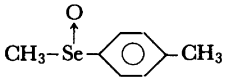
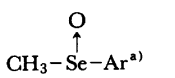
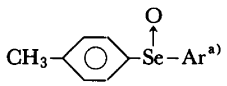
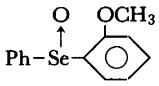
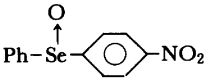
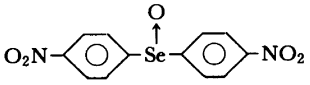
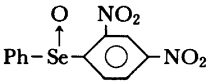
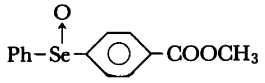
to a stirred solution of the selenide at −25 °C. Stirring continued for 40 min at −25 °C. The mixture was hydrolyzed by an addition of a sodium hydroxide solution. Results are shown in Table 1. By the present method, 4,4′-dinitrodiphenyl selenide (**1g**), which could not be oxidized by sodium periodate,[4] was oxidized to 4,4′-dinitrodiphenyl selenoxide (**2g**) in 90% yield. Nitro-substituted diaryl selenides (**1f** and **1h**) were also oxidized to the corresponding selenoxides (**2f** and **2h**) in good yields, respectively. Methyl *p*-(phenylseleno)benzoate (**1i**), which possesses an electron-withdrawing carboxyl group on an aromatic ring, was similarly oxidized to the corresponding selenoxide **2i** in good yields. By oxidation with sodium periodate, **1i** gave **2i** in only 22% yield. Even selenoxides (**2c** and **2d**) with bulky substituents were obtained in good yields. An undesired oxidation of selenoxide to selenone was not occur with the present method. Both methanol and pyridine play important roles to ensure good yields of selenoxides, since the yield of 4,4′-dinitrodiphenyl selenoxide (**2g**) decreases in the absence of pyridine (Table 2). Also, the yields of 4,4′-dinitrodiphenyl selenoxide (**2g**) and 2,4-dinitrodiphenyl selenoxide (**2h**) were greatly decreased in the absence of both methanol and pyridine. The present reaction is thought to proceed via an intermediary selenonium salt **5**. The formation of this type of



Scheme 2.

selenonium salt was reported in a reaction of diphenyl selenide with *t*-butyl hypochlorite.[10] An equilibrium seems to exist among the starting materials, **3**, selenurane **4** and **5**. The addition of excess methanol and pyridine may cause a shift the equilibrium toward the right, resulting in the formation of a selenonium salt

Table 1. Oxidation of Selenides to Selenoxides

	Product	Reaction Conditions: Solvent	Reaction temperature	Reaction time/min	Selenoxides: Yield %	MS. m/z (M^+) (^{80}Se)	Mp θ_m/°C	IR (KBr) (Se=O) (cm^{-1})
(2a)		CH_3CN	−25°C	40	80	188	—[b]	810 (neat)
(2b)		CH_3CN	−25°C	40	93	202	106—107.5	810
(2c)		CH_3CN CH_2Cl_2 CH_2Cl_2	−25°C −25°C r.t.	40 40 60	90 94 66	314	153.5—155[c]	810
(2d)		CH_3CN	−25°C	40	91	390	147—148.5	820
(2e)		CH_3CN	−25°C	40	99	280	133.5—134.5	820
(2f)		CH_2Cl_2 CH_3CN	−40°C −25°C	40 40	98 93	295	134.5—135.5	825
(2g)		CH_2Cl_2	−25°C	40	90	340	207.5—208.5[d]	830
(2h)		CH_2Cl_2	−25°C	40	94	340	134.5 (decomp)	830
(2i)		CH_3CN CH_2Cl_2	−25°C −25°C	40 40	94 96	308	160—161	825

a) Ar=2,4,6-triisopropylphenyl. b) Isolated as an oil. 53—54°C (reported[9]). c) 136—138°C (reported[8]). d) 206°C (reported[4]).

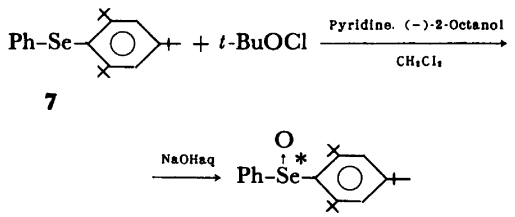
Table 2. Oxidation of Selenides to Selenoxides in the Absence of Pyridine and Methanol[a]

Product	Solvent	Pyridine / Selenide[b]	Methanol / Selenide[b]	Yield %
(2b)	CH_3CN	1	1.2	93
	CH_3CN	—	—	98
(2g)	CH_2Cl_2	1	>2	90
	CH_2Cl_2	—	>2	51[c]
	CH_2Cl_2	—	—	33[d]
(2h)	CH_2Cl_2	1	>2	94
	CH_2Cl_2	—	—	71[e]
(2i)	CH_2Cl_2	1	>2	96
	CH_2Cl_2	—	—	94

a) All reactions were carried out at −25°C and for 40 min. b) mol mol^{-1}. c) 44% of selenide was recovered. d) 60% of selenide was recovered. e) 13% of selenide was recovered.

6, the hydrolysis of which gives selenoxide **2** in good yield.

Recently, Davis et al. reported the synthesis of partially optically active selenoxides by kinetic differentiation during the formation of selenimides.[8] We have attempted to synthesize the optically active selenoxide, the selenium moiety of which was flanged by two bulky substituents to prevent racemization, by an application of the present oxidation method. To a solution of 2,4,6-tri-*t*-butyldiphenyl selenide (**7**) in dry dichloromethane was added equimolar pyridine and excess amounts of (−)-2-octanol (twentyfold of the selenide). An equimolar *t*-butyl hypochlorite in dichloromethane was slowly added to the stirred solution at −40°C. Stirring continued for 2 h at −40°C. After hydrolysis and extraction, (−)-2-octanol was removed in vacuo (30°C/10^{-3}—10^{-4} mmHg (1 mmHg=133.322pa)) and the remaining selenoxide **8** was recrystallized from dichloromethane–hexane. Mp 133.5—134°C. $[\alpha]_D^{32}$ +1.73° (*c* 0.948, CH_2Cl_2). The CD spectrum shows the positive Cotton effect at 291 nm. An enantiomeric excess



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of 1.0% was estimated by HPLC using an optically active column. This enantioselectivity suggests the presence of (−)-1-methylheptyloxyselenonium salt as an intermediate. When (+)-2-octanol was used, selenoxide with a negative optical rotation ($[\alpha]_D^{33}$ −0.428°) was obtained. The racemization of **8** was found to be very slow in neutral solvents at room temperature.

Experimental

All melting points were determined on a Yamato MP-21. IR spectra were recorded on a Hitachi 260-10 spectrometer, ^{1}H-NMR spectra with TMS as an internal standard on a JEOL JNM-PMX60$_{SI}$, CD spectrum on a JASCO J-40A, and Mass spectra on a JEOL JMS-DX300 mass spectrometer. The optical rotation was measured on a JASCO DIP-140 digital polarimeter. Silica-gel TLC and column chromatography were performed on a Merck Kieselgel 60F$_{254}$ and a Wako Wakogel C-200, respectively. Organic solvents were purified and dried by the usual procedures.

Materials. The starting materials (**1a**, **1b**, **1c**, **1f**, **1g**, and **1h**) are all well known compounds.[8,11-14]

***p*-Tolyl 2,4,6-Triisopropylphenyl Selenide (1d):** Compound **1d** was prepared from bis(2,4,6-triisopropylphenyl)-diselenide and *p*-tolylmagnesium bromide. Yield=68%. Mp 59.5—61 °C. IR (KBr) ν=800, 1015, 1560, 1590, 2800—3100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=1.08 (12H, d, J=6.6 Hz, CH_3 of ortho isopropyl), 1.22 (6H, d, J=6.6 Hz, CH_3 of para isopropyl), 2.16 (3H, s, CH_3 of tolyl), 2.4—3.0 (1H, m, para methine), 3.66 (2H, hep., J=6.6 Hz, ortho methine), 6.90 (4H, s, aromatic protons of tolyl), 7.03 (2H, s, aromatic protons of triisopropylphenyl). Found: m/z 374.1512 (^{80}Se), Calcd for $C_{22}H_{30}{}^{80}Se$: 374.1512.

2-Methoxydiphenyl Selenide (1e): Compound **1e** was prepared from diphenyl diselenide and *o*-methoxyphenyl-magnesium bromide. Yield=59%. Bp 143—145 °C/2 mmHg. IR (liq. firm) ν=740, 1020, 1245, 1470, 1575, 2800—3100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=3.78 (3H, s, CH_3), 6.6—7.7 (9H, m, aromatic protons). Found: m/z 264.0076 (^{80}Se), Calcd for $C_{13}H_{12}O^{80}Se$: 264.0053.

Methyl *p*-(Phenylseleno)benzoate (1i): Compound **1i** was prepared by the esterification of *p*-(phenylseleno)-benzoic acid which was obtained by a reaction of benzeneselenol, potassium hydroxide and *p*-iodobenzoic acid.[15] Yield=67%. Mp 78—79 °C. IR (KBr) ν=1700(C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=3.85 (3H, s, OCH_3), 7.2—7.7 (5H, m, aromatic protons of phenyl), 7.32 and 7.83 (4H, ABq, J= 8.2 Hz, aromatic protons of *p*-substituted benzene ring). Found: m/z 292.0002 (^{80}Se), Calcd for $C_{14}H_{12}O_2{}^{80}Se$: 292.0002.

2,4,6-Tri-*t*-butyldiphenyl Selenide (7): Compound **7** was prepared by a reaction of 2,4,6-tri-*t*-butylphenyllithium and benzeneselenenyl bromide in THF and purified by recrystallization from hexane–ethanol. Yield=28% (based on 2,4,6-tri-*t*-butyl-1-bromobenzene). Mp 127.5—128 °C. IR (KBr) ν=730, 1470, 2800—3000 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ= 1.35 (9H, s, para *t*-butyl), 1.48 (18H, s, ortho *t*-butyl), 6.4—7.1 (5H, m, aromatic protons of phenyl), 7.49 (2H, s, aromatic protons of tri-*t*-butylphenyl). Found: m/z 402.1812 (^{80}Se), Calcd for $C_{24}H_{34}{}^{80}Se$: 402.1825.

Typical Procedure for the Oxidation of Selenide. To a solution of selenide (1.0 mmol) in dichloromethane (30 ml) was added an equimolar pyridine and an excess amount of methanol (ca.5 mmol). The solution was cooled to −25 °C under dry nitrogen. An equimolar *t*-butyl hypochlorite in dichloromethane (5 ml) was slowly added to the stirred solution and stirring continued for 40 min at −25 °C. A sodium hydroxide solution (2 mmol in 5 ml of water) was added to the mixture at this temperature with stirring. Then, the resulting mixture was allowed to become room temperature and the organic layer was separated. The aqueous phase was extracted with dichloromethane. The combined organic extract was concentrated and the remaining product was purified either by silica-gel column chromatography or by recrystallization. When acetonitrile was used as a solvent, extraction was carried out after the evaporation of acetonitrile. Among the resulting selenoxides, **2a**, **2c**, and **2g** are known compounds.[5,8,9]

Methyl *p*-Tolyl Selenoxide (2b): Mp 106—107.5 °C. IR (KBr) ν=810 (Se=O), 1400, 1490, 2900—3100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=2.34 (3H, s, CH_3 of tolyl), 2.51 (3H, s, CH_3–Se), 7.25 and 7.55 (4H, ABq, J=8.4 Hz, aromatic protons). Found: m/z 201.9892 (^{80}Se), Calcd for $C_8H_{10}O^{80}Se$: 201.9896.

***p*-Tolyl 2,4,6-Triisopropylphenyl Selenoxide (2d):** Mp 147—148.5 °C. IR (KBr) ν=810, 820(Se=O), 1460, 2850—3000 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=0.88, 1.18, 1.22 (18H, d, J=6.6 Hz, CH_3 of isopropyl), 2.30 (3H, s, CH_3 of tolyl), 2.5—3.1 (1H, m, para methine), 3.72 (2H, hep., J=6.6 Hz, ortho methine), 7.01 (2H, s, aromatic protons of triisopropyl-phenyl), 7.18 and 7.42 (4H, ABq, J=8.1 Hz, aromatic protons of tolyl). Found: m/z 390.1464 (^{80}Se), Calcd for $C_{22}H_{30}O^{80}Se$: 390.1461.

2-Methoxydiphenyl Selenoxide (2e): Mp 133.5—134.5 °C. IR (KBr) ν=770, 820(Se=O), 1020, 1040, 1230, 1270, 1310, 1470 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=3.81 (3H, s, CH_3), 6.8—8.0 (9H, m, aromatic protons). Found: m/z 279.9977 (^{80}Se), Calcd for $C_{13}H_{12}O_2{}^{80}Se$: 280.0002.

4-Nitrodiphenyl Selenoxide (2f): Mp 134.5—135.5 °C. IR (KBr) ν=744, 825(Se=O), 847, 1344(NO_2), 1516(NO_2)cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=7.3—7.8 (5H, m, aromatic protons of phenyl), 7.82 and 8.22 (4H, ABq, J=9.0 Hz, aromatic protons of nitrophenyl). Found: m/z 294.9753 (^{80}Se), Calcd for $C_{12}H_9NO_3{}^{80}Se$: 294.9747.

2,4-Dinitrodiphenyl Selenoxide (2h): Mp 134.5 °C(decomp). IR (KBr) ν=730, 830(Se=O), 915, 1079, 1340(NO_2), 1526(NO_2), 1602 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=7.3—7.9 (5H, m, aromatic protons of phenyl), 8.7—9.1 (3H, m, aromatic protons of dinitrophenyl). Found: m/z 339.9662 (^{80}Se), Calcd for $C_{12}H_8N_2O_5{}^{80}Se$: 339.9598.

Methyl *p*-(Phenylseleninyl)benzoate (2i): Mp 160—161 °C. IR (KBr) ν=739, 761, 825(Se=O), 1204, 1269, 1435, 1585, 1724(C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=3.92 (3H, s, OCH_3), 7.4—7.6 (5H, m, aromatic protons of phenyl), 7.81 and 8.15 (4H, ABq, J=7.6 Hz, aromatic protons of *p*-(methoxycarbonyl)phenyl). Found: m/z 307.9933 (^{80}Se), Calcd for $C_{14}H_{12}O_3{}^{80}Se$: 307.9951.

(+)-2,4,6-Tri-*t*-butyldiphenyl Selenoxide (8): To a solution of 2,4,6-tri-*t*-butyldiphenyl selenide (**7**) (0.75 mmol) in dry dichloromethane (13 ml), was added equimolar pyridine and an excess amount of (−)-2-octanol (15 mmol). The solution was cooled to −40 °C under dry nitrogen. An equimolar *t*-butyl hypochlorite (0.75 mmol) in dry dichloromethane (2 ml) was slowly added to the stirred solution and stirring was continued for 2 h at −40 °C. A sodium hydroxide solution (1.5 mmol in 5 ml of water) was added to the mixture at this temperature with stirring.

Then, the resulting mixture was allowed to become room temperature and the organic layer was separated. The aqueous phase was extracted with dichloromethane. The resulting selenoxide **8** was purified by recrystallization from dichloromethane–hexane after the removal of (−)-2-octanol in vacuo (30 °C/10^{-3}—10^{-4} mmHg). Chemical Yield=54%. Mp 133.5—134 °C. $[\alpha]_D^{32}$ +1.73 °(*c* 0.948, CH_2Cl_2). $[\theta]_{291}$ +236 (Methanol). IR (KBr) ν=745, 840(Se=O), 1360, 1585, 2800—3100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ=1.35 (9H, s, para *t*-butyl), 1.45 (18H, s, ortho *t*-butyl), 6.7—7.3 (5H, m, aromatic protons of phenyl), 7.46 (2H, s, aromatic protons of tri-*t*-butylphenyl). Found: *m/z* 418.1818 (^{80}Se), Calcd for $C_{24}H_{34}O^{80}Se$: 418.1774. The enantiomeric excess was determined by HPLC on an optically active column (Bakerbond chiral phase HPLC column DNBPG/Aminopropylsilica; 25 cm×4.6 mm; using hexane: 2-propanol=95:5 as eluent.

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