The Convenient Syntheses of Organoselenium Reagents

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Many organoselenium compounds are useful reagents or synthons in organic synthesis[1,2]. Among them, dimethyl selenide and its oxide, dimethyl and diphenyl diselenides, and bis- and tris[methylseleno]-methanes as well as bis- and tris[phenylseleno]-methanes possess particular importance. The aim of our work was to elaborate versalite and unexpensive methods for the preparation of the above mentioned compounds on a molar scale. The simplest preparation of dialkyl diselenides is the alkylation of diselenide anion. Because of its great nucleophilicity, diselenide anion reacts readily with a variety of alkylating agents; it is generated either by reaction of selenide anion with one equivalent of selenium or by reduction of selenium with one equivalent of reducing agent. Commonly used reagents for the reduction of selenium are alkali metals in liquid ammonia[3,4], sodium hydroxymethanesulfinate (Rongalite) in water[5,6], sodium borohydride in ethanol or water[7], lithium triethylborohydride in tetrahydrofuran[8], and tetraalkylammonium borohydride in toluene[9]. In a similar manner, dialkyl selenides have been prepared from sodium selenide and alkylating agents[6]. Alkyl halides also react with selenourea to give isoselenouronium salts which can be hydrolyzed with alkali in the presence of more alkyl halide to give symmetrical dialkyl selenides[10]. The most general method for the synthesis of symmetrical and unsymmetrical dialkyl selenides is a Williamson-type approach consisting of the reaction of the sodium salt of an alkaneselenol with alkyl halides[2,11]. Nevertheless, all these methods suffer from some disadvantages: the reducing agents are often expensive and performance of the reaction may be troublesome, in particular, in large-scale preparations.

We have now found that hydrazine hydrate or hydrazine salts of inorganic acids react smoothly with selenium in strong basic media to give diselenide anion in good yield. The reaction proceeds in water and in all solvents unreactive toward strong bases and nucleophiles. It is worthy of note that selenium has also been used for oxidation of hydrazine to diazene[12]. Our method which is outlined in the following scheme is applicable to the preparation of various dialkyl diselenides (**2**) from alkyl halides or alkyl sulfates (**1**).

$$4\ \mathrm{Se} + \mathrm{N_2H_4} + 4\ \mathrm{NaOH} \longrightarrow 2\ \mathrm{Na_2Se_2} + 4\ \mathrm{H_2O} + \mathrm{N_2}$$

$$\mathrm{Na_2Se_2} + 2\ \underset{\mathbf{1}}{\mathrm{R{-}X}} \longrightarrow \underset{\mathbf{2}}{\mathrm{R{-}Se{-}Se{-}R}} + 2\ \mathrm{NaX}$$

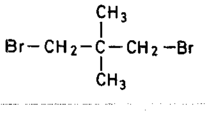
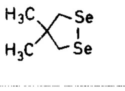
R = alkyl
X = Cl, Br, J, $\mathrm{O{-}SO_2{-}OCH_3}$

The syntheses of compounds **2** were performed on 0.1–1.0 mol scales. The simple procedure described here seems to be more convenient and more efficient than the procedures hitherto reported[6,8,13–16].

Attempts to reduce selenium to selenide ion by hydrazine were unsuccessful. However, we found that dimethyl diselenide (**2a**) and diphenyl diselenide (**2g**) can be quantitatively reduced to methaneselenolate anion (salt **3a**) and phenylselenide anion (salt **3g**), respectively, using hydrazine in aprotic solvents such as dimethylformamide, diethyl ether, tetrahydrofuran, benzene, hexane, etc. The reaction proceeds smoothly at room temperature in the presence of small amounts of tetraalkylammonium chlorides or without catalyst if dimethylsulfoxide is used as solvent. The anions thus formed react readily with various alkylating agents (mono-, di-, tri-, and tetrahalomethanes) to give dialkyl selenides (**4a**) or other selenylmethane derivatives (**5a**, **5g**, **6g**).

In the case R = $\mathrm{CH_3}$, dimethyl diselenide (**2a**) is formed *in situ* and reduced and methylated in a one-pot procedure. Since the reaction of selenolates **3** with alkylating agents such as alkyl halides and alkyl sulfates is obvious and, except for dimethyl selenide (**4a**)[2,18], of only little preparative importance, we investigated the reaction of selenolates **3** with di- and trihalomethanes. The products obtained from these reactions are bis[methylseleno]-methane (**5a**), bis[phenylseleno]-methane (**5g**), and tris[phenylseleno]-methane (**6g**). These compounds are useful synthons[2,16,19–22]. The method for their synthesis described here is simpler and more efficient than the above cited methods.

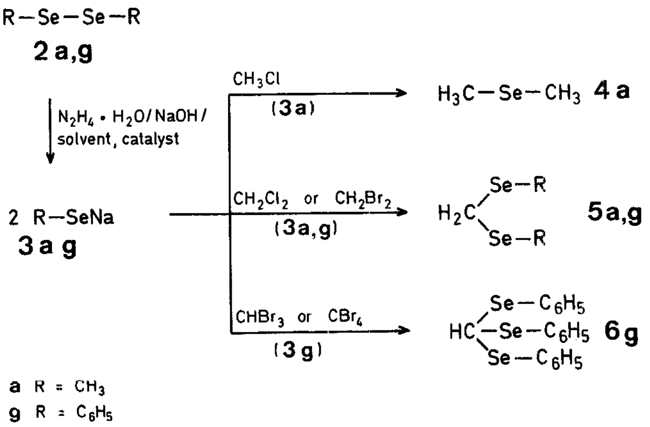
Table 1. Preparation of Dialkyl Diselenides (**2**)

Sol-vent	Redu-cing agent[a]	Molar ratio Se: N_2H_4	Alkylating agent	Product Formula	Yield[b] [%]	m.p. or b.p./torr [°C]		^{1}H-N.M.R. (CCl_4/$HMDSO_{ext}$) δ [ppm]
						found	reported	
water	A	1:1	H_3C-J	**a** $H_3C-Se-Se-CH_3$	79	b.p. 156–158°/760	b.p. 155–157°[14]	2.26 (s, 6H, $2CH_3$)
water	A	1:1	$(H_3CO)_2SO_2$		69			
water	B	1:1	H_3C-J		78			
methanol	A	2:1	H_3C-J		78			
DMF	C	4:1	H_3C-Br		88			
DMSO	C	4:1	H_3C-Br		84			
petrol-eum ether	C	2:1	H_3C-J		83			
DMF	C	4:1	$C_6H_5-CH_2-Cl$	**b** $C_6H_5-CH_2-Se-Se-CH_2-C_6H_5$	75	m.p. 91–92°	m.p. 92°[15]	4.04 (s, 4H, $2CH_2$); 7.5 (m, 10H_{arom})
DMF	C	4:1	i-C_3H_7-Br	**c** i-$C_3H_7-Se-Se-C_3H_7$-i	89	b.p. 110°/2	b.p. 111–119°/6–8[14]	1.74 (d, 12H, J = 8 Hz, $4CH_3$); 3.50 [quin, 2H, J = 8 Hz, $2C\underline{H}(CH_3)_2$]
DMF	C	4:1	n-C_4H_9-Cl	**d** n-$C_4H_9-Se-Se-C_4H_9$-n	91	b.p. 94°/18	b.p. 58°/5[15]	1.26 (t, 6H, J = 6 Hz, $2CH_3$); 1.62–2.18 (m, 8H, $4CH_2$); 3.19 (t, 4H, J = 8 Hz, CH_2-Se)
DMF	C	4:1	n-$C_6H_{11}-Br$	**e** n-$C_6H_{11}-Se-Se-C_6H_{11}$-$n$	80	b.p. 130°/0.8	b.p. 158°/3[15]	1.6–2.5 (m, 20H, $10CH_2$); 3.15 (m, 2H, $C\underline{H}-Se-Se-C\underline{H}$)
DMF	C	4:1	 $Br-CH_2-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-Br$	**f** 	68	m.p. 34–35°	—[c, 20]	1.64 (s, 6H, $2CH_3$); 2.38 (s, 4H, $2CH_2$)

[a] A = $N_2H_4 \cdot H_2O$ (80%); B = $N_2H_4 \cdot H_2SO_4$; C = $N_2H_4 \cdot H_2O$ (100%).

[b] Yields are based on selenium.

[c] Only ^{1}H-N.M.R. data were reported in Ref.[20].



We have also found that diselenide anion obtained by reduction of selenium with hydrazine is smoothly further reduced to the selenide anion by sodium dithionite in aqueous medium. On the basis of these findings, we elaborated a convenient procedure for the preparation of dimethyl selenide (**4a**); for this particular purpose, this procedure seems to be better than the general methods described for the preparation of compounds **5** and **6**.

$$4\,Se + N_2H_4 + 4\,NaOH \longrightarrow 2\,Na_2Se_2 + 4\,H_2O + N_2$$

$$Na_2Se_2 + Na_2S_2O_4 + 4\,NaOH \longrightarrow$$

$$2\,Na_2Se + 2\,Na_2SO_3 + 2\,H_2O$$

$$Na_2Se + 2\,H_3C-X \longrightarrow H_3C-Se-CH_3 + 2\,NaX$$

Dimethyl selenide (**4a**) can be easily oxidized to dimethyl selenoxide (**7a**) in 93% yield of pure product using 30% aqueous hydrogen peroxide at −10°C. Compound **7a**

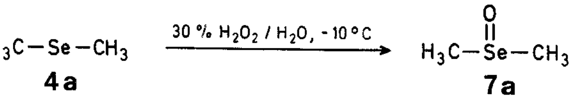
Table 2. Reaction of Selenolate Anions **3a,g** with Halomethanes

Solvent	Catalyst[a]	Halomethane	Product	Yield[b] [%]	m.p. or b.p./torr [°C] found	m.p. or b.p./torr [°C] reported	^{1}H-N.M.R. ($CCl_4/HMDS_{ext}$) δ [ppm]
DMF	A	CH_3Cl	**4a**	81	b.p. 57°/760	b.p. 56–58°[23]	2.26 (s, 6H, 2CH_3)
DMSO	–	CH_3Cl		63			
decalin	B	CH_3Cl		91			
DMF	A	CH_2Cl_2	**5a**	93	b.p. 75°/15	b.p. 80°/15[19]	2.34 (s, 2H, CH_2); 3.85 (s, 2H, CH_2)
THF or ether	B	CH_2Cl_2		91			
pentane	B	CH_2Cl_2		93			
DMF	–	CH_2Cl_2	**5g**	96	m.p. 36–38°	m.p. 30.0–30.6°[19]	4.12 (s, 2H, CH_2); 7.42–7.58 (m, 6H_{arom}); 7.68–7.80 (m, 4H_{arom})
THF or ether	B	CH_2Cl_2		90			
pentane	B	CH_2Cl_2 or CH_2Br_2		95			
DMF	–	$CHBr_3$	**6g**	78	m.p. 98–99°	m.p. 90.5–91.5°[20]	5.58 (s, 1H, CH); 7.50–7.58 (m, 9H_{arom}); 7.74–7.84 (m, 6H_{arom})
DMF	–	CBr_4		69			
pentane	B	$CHBr_3$		86			

[a] A = Tetraethylammonium chloride; B = Tetrabutylammonium chloride.

[b] Yields are based on selenium or other selenium substrates.

which is a mild and selective oxidizing agent[24,25,26] has previously been prepared by less convenient methods such as oxidation of dimethyl selenide with ozone at −50 °C or by treating dimethylselenium dibromide with silver oxide in methanol[6,27,28].



$$\underset{\textbf{4a}}{H_3C-Se-CH_3} \xrightarrow{30\%\ H_2O_2\ /\ H_2O,\ -10\,°C} \underset{\textbf{7a}}{H_3C-\overset{O}{\overset{\|}{Se}}-CH_3}$$

Melting points were determined in capillary tubes. M.p.s and b.p.s are uncorrected. ^{1}H-N.M.R. spectra were recorded on a Tesla 100 MHz instrument using hexamethyldisiloxane (HMDSO) as external standard.

Dimethyl Diselenide (2a); Preparation in Aqueous Medium:

Selenium (79 g, 1 g-atom) is added to a stirred solution of sodium hydroxide (60 g, 1.5 mol) in water (300 ml). The mixture is cooled in a water bath, and 80% hydrazine hydrate (65 g, 1.04 mol) is added over 30 min, and stirring is continued for an additional 5–7 h at room temperature. Iodomethane (142 g, 1 mol) or dimethyl sulfate (126 g, 1 mol) is then added dropwise over a period of 2–3 h. During the addition, the temperature is maintained at 15–20 °C. The end point of the methylation is indicated by a sharp color change from dark red to yellow. The mixture was is then stirred for 20 min, diluted with water (~ 1000 ml), and extracted with dichloromethane (3 × 100 ml). The organic layer is washed with water (2 × 300 ml), dried with magnesium sulfate, and evaporated. The residual product is distilled through a 7 cm Vigreux column; yield: see Table 1; b.p. 156–158 °C/760 torr.

The above procedure can also be performed with hydrazine sulfate in place of hydrazine hydrate; in this case, the amount of sodium hydroxide must be increased by 2 mol per mol of hydrazine sulfate.

The same procedure is used for performance of the reaction in methanol.

Dialkyl Diselenides (2a–f); Preparation in Dimethylformamide:

To a vigorously stirred mixture of powdered sodium hydroxide (3.0 g, 75 mmol), selenium (4.0 g, 50 mmol), and dimethylformamide (50 ml), 100% hydrazine hydrate (0.7 ml, 14 mmol) is added dropwise at 15–20 °C. The mixture is stirred for 6 h at room temperature and then a solution of the methylating agent (100 mmol) in dimethylformamide (15 ml) is added dropwise over a 30–60 min period. There is an abrupt color change from deep green to light brown as methylation comes to the end. The mixture is diluted with water (~ 250 ml) and extracted with dichloromethane (3 × 50 ml). The organic layer is washed with 6 normal hydrochloric acid (50 ml) and with water (100 ml) and is dried with magnesium sulfate. The solvent is evaporated and the residue distilled (**2a–e**) or purified by column chromatography on silica gel (pentane/dichloromethane 4/1 as eluent) and recrystallization from hexane (**2f**).

Dimethyl Selenide (4a); Preparation in Different Solvents:

in Decalin: In a water-cooled 2000 ml round-bottom flask equipped with an efficient stirrer, a gas inlet, and a dropping funnel are placed powdered sodium hydroxide (80 g, 2 mol) and freshly distilled decalin (150 ml). The mixture is vigorously stirred and 100% hydrazine hydrate (25 ml, 0.5 mol) is added dropwise, followed by the slow addition of Triton X-100 (10 g). Then, selenium (79 g, 1 g-atom) is added portionwise and stirring is continued for 30 min. Thereafter, a stream of chloromethane is passed under the surface of the mixture over a 2 h period [55 g (1.1 mol) of chloromethane are consumed during this time]. Powdered sodium hydroxide (60 g, 1.5 mol) and tetrabutylammonium chloride (6.3 g, 23 mmol) are then added, followed by the dropwise addition of a second portion of 100% hydrazine hydrate (25 ml, 0.5 mol) over a 1 h period. After the addition, a slow stream of chloromethane is passed into the solution for 4.5 h [75 g (1.5 mol) of CH_3Cl are consumed]. The mixture is stirred for an additional 30 min, diluted with water to a volume of ~ 1500 ml, and distilled. The distillate is collected until the temperature of the vapor has reached 98 °C. The organic layer of the distillate is separated, dried with magnesium sulfate, and redistilled through a Vigreux column.

in DMF: To a vigorously stirred suspension of powdered sodium hydroxide (30 g, 0.75 mol) and selenium (39.5 g, 0.5 mol) in dimethylformamide (250 ml), 80% hydrazine hydrate (10 ml, 0.16 mol) is added dropwise over 30 min at room temperature. Stirring is continued for 5.5 h and the mixture then allowed to stand overnight. Stirring is again started and chloromethane is passed into the mixture at 15–20 °C (external cooling). After the reaction mixture has became yellow (~ 1 h), tetraethylammonium chloride (6.6 g, 40 mmol) and sodium hydroxide pellets (40 g, 1 mol) are added and a next portion of 80% hydrazine hydrate (15 g, 0.24 mol) is added dropwise. Then, chloromethane is passed into the mixture at a much lower rate until the yellow mixture has become off-white (~ 5.5 h) [a total of 58 g (1.16 mol) of CH_3Cl has then been consumed]. The mixture is diluted with water to a volume of ~ 2000 ml and distilled. The distillate is collected until the temperature of the vapor has reached 98 °C. The organic layer of the distillate is separated, washed with 6 normal hydrochloric acid (50 ml) and with water (100 ml), dried with magnesium sulfate, and redistilled.

in DMSO: The procedure is essentially the same as that using DMF except that the addition of tetraethylammonium chloride is omitted.

in Water: Selenium (79 g, 1 g-atom) is added to a stirred solution of sodium hydroxide (120 g, 3 mol) in water (500 ml) cooled in a water bath. To this mixture, 80% hydrazine hydrate (70 g, 1.12 mol) is added dropwise, with continued cooling, over a 15 min period. The mixture is stirred for 5.5 h at room temperature, and allowed to stand overnight. It is then diluted with water (1000 ml) and sodium dithionite is added portionwise until the red mixture has become off-white [total consume of 85% sodium dithionite: 260 g (1.05 mol)]. During the addition, the mixture is vigorously stirred and cooled with ice. After the addition, the temperature is lowered to − 10 °C and bromomethane (200 g, 2.1 mol) is introduced through a Dry Ice condenser over a 6 h period at − 10 to − 5 °C. The cooling bath is removed, the mixture is heated, and the volalite components are distilled off together with some water. The organic layer of the condensate is separated, dried with magnesium sulfate, and redistilled through a Vigreux column.

Dimethyl Selenoxide (7a):

A 150 ml round bottomed flask fitted with stirrer and dropping funnel is charged with 30% aqueous hydrogen peroxide (25 ml, 0.24 mol) and cooled in an ice/salt bath. Dimethyl selenide (22 g, 0.2 mol) is added dropwise over 1–1.5 h and stirring and cooling is continued for 30 min. The mixture is then concentrated on a rotatory evaporator. Excessive heating during evaporation should be avoided; maximum bath temperature: 60 °C. Dichloromethane or chloroform (80 ml) and anhydrous potassium carbonate (30 g) are added to the oily residue. The next day, pottasium carbonate is filtered off, washed thoroughly with the solvent, and the solvent is removed from the filtrate under reduced pressure to leave a colorless solid. This latter drying procedure is repeated with dichloromethane or chloroform (60 ml) and potassium carbonate (15 g). The flask containing the crystalline product (after the second evaporation) is placed in a vacuum desiccator over phosphorus pentoxide at 15–20 torr for 15–20 h. The crude product is recrystallized from dry benzene (40 ml) and dried in vacuo over phosphorus pentoxide to give pure **7a** as colorless needles; yield: 22.3 g (93%); m.p. (in sealed capillary): 92–94 °C (Ref.[23], m.p. 91–93 °C).

^{1}H-N.M.R. ($CDCl_3/HMDSO_{ext}$): $\delta = 3.05$ ppm (s, 6H, $2CH_3$).

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Bis[methylseleno]-methane (5a), Bis[phenylseleno]-methane (5g), and Tris[phenylseleno]-methane (6g); General Procedures:

in THF, Ether, or Pentane: To a vigorously stirred mixture of powdered sodium hydroxide (10 g, 250 mmol), tetrabuthylammonium chloride (2.8 g, 10 mmol), dimethyl diselenide or diphenyl diselenide (50 mmol), and solvent (80 ml), 100% hydrazine hydrate (3 ml, 60 mmol) is added dropwise at room temperature. Stirring is continued for 30 min, then a solution of the dihalomethane (60 mmol) or trihalomethane (35 mmol) in the same solvent (10 ml) is added dropwise over 1 h and stirring is continued for 1 h. Water (150 ml) is then added and the mixture extracted with dichloromethane (3 × 50 ml). The extract is dried with magnesium sulfate, the solvent evaporated in vacuo, and the residual product purified by column chromatography on silica gel (petroleum ether/chloroform 4/1 as eluent). Product **5a** is distilled under reduced pressure; product **5g** is recrystallized from ethanol and product **6g** from hexane.

in DMF: To a vigorously stirred mixture of powdered sodium hydroxide (10 g, 250 mmol), tetraethylammonium chloride (1.7 g, 10 mmol, only for **5a**; in the preparation of **5g** and **6g**, no catalyst is used), dimethyl diselenide (9.4 g, 50 mmol) or diphenyl diselenide (15.6 g, 50 mmol), and dimethylformamide (100 ml), a solution of hydrazine hydrate (7.5 ml, 150 mmol, for **5a**; 3.0 ml, 60 mmol, for **5g** and **6g**) in dimethylformamide (20 ml) is added dropwise over 1 h (**5a**) or over 2.5 h (**5g**, **6g**). A solution of the dihalomethane (60 mmol) in dimethylformamide (10 ml) is then added dropwise over 1 h in the case of **5a**; for the preparation of **5g** and **6g**, the mixture is stirred at 50 °C while a solution of the dihalomethane (60 mmol) or trihalomethane (35 mmol) is added over 20 min, and the temperature of the mixture then slowly raised to 60 °C for 1 h. The mixture is then diluted with water (300 ml) and extracted with dichloromethane (3 × 50 ml). The organic extract is washed with 6 normal hydrochloric acid and with water (200 ml) and is dried with magnesium sulfate. The solvent is removed in vacuo and the residual product purified by column chromatography on silica gel (petroleum ether/chloroform 4/1 as eluent). Product **5a** is distilled under reduced pressure; product **5g** is recrystallized from ethanol and product **6g** from hexane.

When the above procedure is performed with tetrabromomethane in place of bromoform compound **6g** is isolated as the sole product; tetrakis[phenylseleno]-methane is not detected.

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