A Convenient Preparation of 3,5-Disubstituted 1,2,4-Selenadiazoles from Primary Selenoamides by Treatment with *N*-Bromosuccinimide

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Synopsis. A convenient preparation of 3,5-disubistituted 1,2,4-selenadiazoles was achieved by treatment of various primary selenoamides with *N*-bromosuccinimide.

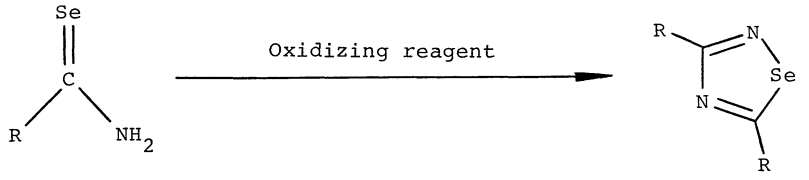
The syntheses and transformation of selenium atom-containing heterocycles are of current interest in organic chemistry, and various methods for the synthesis of these compounds have been reported within the past several years;[1-6] nonetheless detailed investigation on the reactivities and the synthetic applications of selenazoles and selenadiazoles has been limited owing to the difficulty in preparation of the selenium-containing starting materials. It has been widely known that the most suitable starting material for these selenium-containing heterocycles are primary selenoamides **1**.[7-9] However, the preparation of these primary selenoamides **1** is impeded by the higher lability of **1** toward bases and oxidants, and few methods have so far been reported.[10-16] Cohen reported the synthesis of **1** from nitriles[15] and the subsequent transformation of **1** to the corresponding 3,5-disubstituted 1,2,4-selenadiazoles **2** by using I_2, but the yields of **2** were modest and the reactions were successful only in the cases of aromatic selenoamides **1**.[7]

In our previous paper we also provided a convenient synthesis of primary aromatic or aliphatic selenoamides, selenourea, and selenothiocarbamate by treatment of the corresponding nitriles, cyanamide, or thiocyanate with $(Me_3Si)_2Se$ in the presence of $BF_3{\cdot}OEt_2$.[17] It was naturally regarded that **1** would act as starting materials for the synthesis of 3,5-disubstituted 1,2,4-selenadiazoles **2** possessing various substituents by treatment with oxidizing reagents.[4,7] In this paper we would like to describe a convenient preparation of 3,5-disubstituted 1,2,4-selenadiazoles **2** by treatment of primary selenoamides **1** with *N*-bromosuccinimide (NBS).

Results and Discussion

A general procedure in the preparation of 3,5-disubstituted 1,2,4-selenadiazoles **2** is as follows. To a $CHCl_3$ solution of primary selenoamides **1**, 1.1 equiv

Table 1. Preparation of 3,5-Disubstituted 1,2,4-Selenadiazoles by Treatment of Selenoamides with Oxidizing Reagents[a]



1 **2**

Run	Substrate/R		Oxidizing reagent (equiv)		Solvent	Temp/°C	Time/h	Yield/% of **2**
1	C_6H_5	(**1a**)	NBS	(1.1)	$CHCl_3$	R.T.	1	76
2	C_6H_5	(**1a**)	DMSO[b]	(Excess)	CH_2Cl_2	R.T.	9	23
3	*p*-$CH_3C_6H_4$	(**1b**)	NBS	(1.1)	$CHCl_3$	R.T.	1	72
4[c]	*p*-$CH_3C_6H_4$	(**1b**)	NBS	(1.1)	CH_2Cl_2	−78	40 min	87
5	*p*-$CH_3C_6H_4$	(**1b**)	30% H_2O_2	(2.0)	MeOH	0	10 min	66
6	*p*-$CH_3OC_6H_4$	(**1c**)	NBS	(1.1)	$CHCl_3$	0	1	70
7	*p*-ClC_6H_4	(**1d**)	NBS	(1.1)	$CHCl_3$	0	1	82
8	$CH_3CH_2CH_2$	(**1e**)	NBS	(1.1)	CH_2Cl_2	−90	6	25
9	$CH_3(CH_2)_3CH_2$	(**1f**)	NBS	(1.1)	CH_2Cl_2	−78	30 min	42
10	$CH_3(CH_2)_5CH_2$	(**1g**)	NBS	(1.1)	CH_2Cl_2	−78	1	63
11	Me_2N	(**1h**)	NBS	(1.2)	CH_2Cl_2	−78	5	36
12	Me_2N	(**1h**)	30% H_2O_2	(2.0)	MeOH	0	30 min	37
13	Me_2N	(**1h**)	MCPBA	(1.2)	MeOH	0	30 min	32
14	$C_6H_5CH_2S$	(**1i**)	NBS	(1.1)	CH_2Cl_2	−90	2	3[d]

a) The corresponding nitriles were obtained in all runs. b) One equiv of 1-methyl-2-chloropyridinium iodide was added. c) Five equiv of styrene was added. d) Benzyl thiocyanate was obtained in 80% yield.

of NBS in $CHCl_3$ was added dropwise under nitrogen atmosphere at 0 °C and stirred for 1 h. The reaction mixture was then quenched with 10% NaOH solution. After the usual work-up and purification by SiO_2 column chromatography, the resulting 3,5-disubstituted 1,2,4-selenadiazoles **2** were isolated in good to moderate yields as air-stable products. These results are shown in Table 1. By-products of the reaction were the corresponding nitriles in all cases owing to the facile selenium-extrusion of **1**. The physical properties of the obtained products **2** possessing aromatic substituents were identical in all respects with those reported by Cohen.[7] The structures of new products **2** having various aliphatic or heteroatom substituents were confirmed by ^1H NMR, IR, MS, and elemental analyses.

New products possessing heteroatom substituents, 3,5-bis(dimethylamino)-1,2,4-selenadiazole **2h** and 3,5-bis(benzylthio)-1,2,4-selenadiazole **2i**, were also obtained by this method. However, the yield of **2h** from *N,N*-dimethylselenourea **1h** was low, and only a trace amount of **2i** was formed from the corresponding selenothiocarbamate **1i** where benzyl thiocyanate was obtained in 80% yield. No improvement in the yield of **2h** could be achieved by using 30% H_2O_2 or MCPBA in place of NBS. The low yield of **2i** by treatment with NBS might be attributed to the higher affinity of the starting materials to the soft oxidizing reagent. Electron-donating substituents such as the dimethylamino group are expected to accelerate the chemical reactivities of 1,2,4-selenadiazole rings toward electrophilic reagents or Diels–Alder reactions,[18,19] and the introduction of such substituents to the rings would afford possibilities for the further conversions of this ring system to several heterocycles.

Other reagents for the oxidative dimerization of **1** were also investigated for the optimization of the preparation of **2**. However, unlike the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles from primary thioamides,[20] treatment of **1a** with DMSO/1-methyl-2-chloropyridinium iodide system was not fully effective for the synthesis of 3,5-dipheyl-1,2,4-selenadiazole **2a** (Run 2 in Table 1). As was successful in the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles, primary selenoamide Se-oxides were also expected to provide 1,2,4-selenadiazoles **2** by treatment with electrophilic reagents such as H^+. Although attempts for the isolation of *p*-methylselenobenzamide Se-oxide by the reaction of *p*-methylselenobenzamide **1b** with 30% H_2O_2 in MeOH at 0 °C were not successful, 3,5-di-*p*-tolyl-1,2,4-selenadiazole **2b**, *p*-methylbenzonitrile, and elemental selenium were obtained in 66, 27, and 64% yields, respectively.

In these reactions, several points are worth nothing: (1) Among the several reagents, NBS gives good results for the synthesis of 1,2,4-selenadiazoles **2** from primary selenoamides **1** except **1h** and **1i**. (2) The yields of 1,2,4-selenadiazoles **2** possessing aromatic substituents were generally high when NBS was used. On the other hand, aliphatic and heteroatom analogues **2** were obtained in moderate to low yields owing to the facile decomposition of selenoamides **1** to nitriles caused by the reagents.

The oxidative dimerization of selenoamides **1** was assumed to proceed via a similar mechanism that form 3,5-disubstituted 1,2,4-thiadiazoles reported previously by us.[20]

Conclusively, we have established a convenient one-step synthesis of 3,5-disubstituted 1,2,4-selenadiazoles **2** by treatment of primary selenoamides **1** with NBS. These products are expected to promote further chemical conversions by the use of reactivities of carbon–selenium or nitrogen–selenium bonds in the aromatic ring as well as the introduction of various functionalities to the 3- and 5-positions of the nucleus. Chemical conversion of 1,2,4-selenadiazoles **2** toward novel heterocyclic ring systems is now in progress in our laboratory.

Experimental

General. The starting selenoamides **1** were prepared by treatment of the corresponding nitriles with $(Me_3Si)_2Se$ in the presence of $BF_3{\cdot}OEt_2$.[17] The other reagents were commercial reagent grade materials and were purified by recrystallization or by distillation prior to use. IR spectra were recorded with a Hitachi 295 infrared spectrophotometer. ^1H NMR spectra were recorded with a Hitachi R-22 (90 MHz) spectrometer in deuteriochloroform solution containing tetramethylsilane as an internal standard. MS spectra were recorded with a Hitachi RMU-6M and Hitachi M-2000 spectrometer, with a direct inlet system, operating at 20 or 70 eV.

General Procedure for the Reaction of Primary Selenoamides 1 with NBS. A typical procedure is described below for the preparation of 3,5-diphenyl-1,2,4-selenadiazole **2a**. A solution of 196 mg (1.1 mmol) of NBS in 50 ml of $CHCl_3$ was added dropwise to a solution of 184 mg (1 mmol) of selenobenzamide **1a** in 50 ml of $CHCl_3$ at room temperature under nitrogen atmosphere, and was stirred for 1 h. The reaction mixture was then quenched with excess amount of 2M NaOH solution (1M=1 mol dm^{-3}). Precipitated elemental selenium was separated by filtration, and the filtrate was extracted with $CHCl_3$. The organic layer was washed with water and dried over anhydrous sodium sulfate. After removal of $CHCl_3$, the residue was purified by SiO_2 column chromatography using benzene as an eluent to give 3,5-diphenyl-1,2,4-selenadiazole **2a** in 76% yield.

2a: Colorless needles; mp 85 °C (lit, 85 °C);[7] IR (KBr) 1515, 1480, 1440, 1420, 1320, 1278, 1218, 1094, 1068, 1025, 1000, 970, 870, 760, and 680 cm^{-1}; ^1H NMR δ=7.43—7.53 (m, 6H), 7.93—8.05 (m, 2H), and 8.34—8.47 (m, 2H).

2b: Colorless needles; mp 122 °C (lit, 122 °C);[7] IR (KBr) 2925, 2830, 1600, 1482, 1410, 1320, 1300, 1280, 1240, 1160, 1090, 1020, 965, and 822 cm^{-1}; ^1H NMR δ=2.37 (s, 3H), 2.38 (s, 3H), 7.33 (d, J=8 Hz, 2H), 7.34 (d, J=8 Hz, 2H), 7.83 (d, J=8 Hz, 2H), and 8.27 (d, J=8 Hz,2H).

2c: Colorless needles; mp 139 °C (lit, 139 °C);[7] IR (KBr) 2925, 2840, 1600, 1485, 1318, 1245, 1165, 1095, 1022, 965, and 822 cm^{-1}; ^1H NMR δ=3.80 (s, 3H), 3.82 (s, 3H), 6.89 (d, J=8 Hz, 2H), 6.95 (d, J=8 Hz, 2H), 7.83 (d, J=8 Hz, 2H), and 8.30 (d, J=8 Hz, 2H).

2d: Colorless needles; mp 168 °C (lit, 168 °C); IR (KBr) 1590, 1510, 1475, 1400, 1310, 1280, 1230, 1165, 1090, 1015, 970, 875, 830, 735, and 685 cm^{-1}; ^1H NMR δ=7.24 (d, J=8 Hz, 4H), 7.87 (d, J=8 Hz, 2H), and 8.27 (d, J=8 Hz, 2H).

2e: Pale yellow oil; MS (m/z, ^{80}Se) 218 (M^+, 1%); IR (neat) 2950, 2860, 1700, 1515, 1450, 1375, 1268, 1195, 1142, 1080, 1052, 1025, 945, and 850 cm^{-1}; ^1H NMR δ=0.98 (t, J=7 Hz,

3H), 1.06 (t, J=7 Hz, 3H), 1.85 (sextet, J=7 Hz, 4H), 2.92 (t, J=7 Hz, 2H), and 3.06 (t, J=7 Hz, 2H). Found: C, 43.53; H, 6.52; N, 12.44%. Calcd for $C_8H_{14}N_2Se$; C, 44.25; H, 6.50; N, 12.90%.

2f: Pale yellow oil; MS (m/z, ^{80}Se) 274 (M^+, 14%); IR (neat) 2920, 2850, 1510, 1450, 1375, 1260, 1190, 1140, 1055, 940, 720, and 580 cm^{-1}; ^1H NMR δ=0.83—0.98 (m, 6H), 1.27—1.99 (m, 12H), 2.94 (t, J=7 Hz, 2H), and 3.07 (t, J=7 Hz, 2H). Found: C, 52.32; H, 8.27; N, 10.10%. Calcd for $C_{12}H_{22}N_2Se$; C, 52.74; H, 8.11; N, 10.25%.

2g: Pale yellow oil; MS (m/z, ^{80}Se) 330 (M^+, 11%); IR (neat) 2920, 2850, 1510, 1450, 1375, 1265, 1140, 1070, and 720 cm^{-1}; ^1H NMR δ=0.80—0.95 (m, 6H), 1.10—1.19 (m, 20H), 2.93 (t, J=7 Hz, 2H), and 3.07 (t, J=7 Hz, 2H). Found: C, 58.01; H, 9.41; N, 8.33%. Calcd for $C_{16}H_{30}N_2Se$: C, 58.34; H, 9.18; N, 8.50%.

2h: Colorless needles; 49—50 °C, MS (m/z, ^{80}Se) 220 (M^+, 99%); IR (KBr) 2910, 2850, 1590, 1510, 1370, 1330, 1250, 1190, 1110, 1050, 1020, 850, and 720 cm^{-1}; ^1H NMR δ=3.08 (s, 6H) and 3.11 (s, 6H). Found: C, 32.83; H, 5.50; N, 26.39%. Calcd for $C_6H_{12}N_4Se$: C, 32.88; H, 5.52; N, 25.57%.

2i: Colorless oil; MS (m/z, ^{80}Se) 378 (M^+); IR (neat) 3040, 2890, 1490, 1440, 1370, 1160, 990, and 690 cm^{-1}; ^1H NMR δ=4.41 (s, 2H), 4.42 (s, 2H), and 7.20—7.45 (m, 10H). Found: C, 50.57; H, 3.71; N, 7.24%. Calcd for $C_{16}H_{14}N_2S_2Se$: C, 50.92; H, 3.74; N, 7.42%.

Preparation of 3,5-Diphenyl-1,2,4-selenadiazole 2a by DMSO/1-Methyl-2-chloropyridinium Iodide. A solution of 7.36 g (40 mmol) of selenobenzamide **1a**, 25 ml of DMSO, and 10.32 g (40 mmol) of 1-methyl-2-chloropyridinium iodide in 300 ml of CH_2Cl_2 under nitrogen atmosphere was stirred at room temperature for 9 h, and the reaction mixture was then filtered. After removal of CH_2Cl_2 and DMSO, the residue was recrystallized from EtOH to give 3,5-diphenyl-1,2,4-selenadiazole **2a** in 23% yield.

Preparation of 3,5-Disubstituted 1,2,4-selenadiazoles 2 by 30% H_2O_2. A typical procedure is described below for the preparation of 3,5-di-*p*-tolyl-1,2,4-selenadiazole **2b**. To a solution of 198 mg (1 mmol) of *p*-methylselenobenzamide **1b** in 20 ml of MeOH, a solution of 227 mg (2 mmol) of H_2O_2 in 5 ml of MeOH was added at 0 °C. Immediately a reddish solid precipitated. The reaction mixture was then separated by filtration to give 153 mg of solid **A**, and the filtrate was extracted with CH_2Cl_2. The organic layer was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by SiO_2 column chromatography using hexane as an eluent to give *p*-methylbenzonitrile in 27% yield. The solid **A** was treated with CH_2Cl_2 to separate 3,5-di-*p*-tolyl-1,2,4-selenadiazole **2b** and elemental selenium in 66 and 64% yields, respectively.

Preparation of 3,5-Bis(dimethylamino)-1,2,4-selenadiazole 2h by MCPBA. To a solution of 151 mg (1 mmol) of *N,N*-dimethylselenourea **1h** in 5 ml of MeOH, a solution of 258 mg (1.2 mmol) of 80% MCPBA in 5 ml of CH_2Cl_2 was added at 0 °C, and stirred for 30 min. The reaction mixture was then quenched with saturated sodium sulfite solution, and extracted with $CHCl_3$. The organic layer was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was separated by SiO_2 column chromatography using hexane/ether (2/1) as an eluent giving 3,5-bis(dimethylamino)-1,2,4-selenadiazole **2h** and dimethylcyanamide in 32 and 23% yields, respectively.

References

1) T. Ueda, Y. Shibata, J. Sakakibara, M. Inoue, and T. Ishida, *Chem. Pharm. Bull.*, **30**, 3424 (1982).
2) M. Yokoyama, K. Kumata, H. Hatanaka, and T. Shiraishi, *Bull. Chem. Soc. Jpn.*, **59**, 2909 (1986).
3) T. Ueda, S. Kawai, and J. Sakakibara, *Chem. Pharm. Bull.*, **35**, 398 (1987).
4) I. Shibuya, *Nippon Kagaku Kaishi*, **1987**, 1691.
5) V. Bertini, A. De Munno, N. Picci, F. Lucchesini, and M. Pocci, *Heterocycles*, **26**, 2153 (1987).
6) M. Renson, "The Chemistry of Organic Selenium and Tellurium Compounds," ed by S. Patai and Z. Rappoport, John Wiley and Sons, Chichester (1986), Vol. 1, p. 399.
7) V. I. Cohen, *Synthesis*, **1978**, 768.
8) V. I. Cohen, *J. Heterocycl. Chem.*, **16**, 365 (1979).
9) V. I. Cohen, *Synthesis*, **1979**, 66.
10) F. v. Dechend, *Chem. Ber.*, **7**, 1273 (1874).
11) K. Kindler, *Liebigs Ann. Chem.*, **431**, 187 (1923).
12) L. G. S. Brooker, G. H. Keyers, and F. L. White, *J. Am. Chem. Soc.*, **57**, 2492 (1935).
13) W. Walter and G. Maerten, *Liebigs Ann. Chem.*, **669**, 66 (1963).
14) K. A. Jensen and P. H. Nielsen, *Acta Chem. Scand.*, **20**, 597 (1966).
15) V. I. Cohen, *Synthesis*, **1978**, 668.
16) A. Ogawa, J. Miyake, Y. Karasaki, S. Murai, and N. Sonoda, *J. Org. Chem.*, **50**, 384 (1985).
17) K. Shimada, S. Hikage, Y. Takeishi, and Y. Takikawa, *Chem. Lett.*, **1990**, 1403.
18) M. P. Cava and L. E. Saris, *J. Chem. Soc., Chem. Commun.*, **1975**, 617.
19) K. T. Potts, F. Huang, and R. K. Khattak, *J. Org. Chem.*, **42**, 1644 (1977).
20) Y. Takikawa, K. Shimada, K. Sato, S. Sato, and S. Takizawa, *Bull. Chem. Soc. Jpn.*, **58**, 995 (1985).