Synthesis of Organoselenium Sulfonamides as New Potential Cytokine Inducers: 2,2′-Diselenobis(benzenesulfonamides) and 1,3,2-Benzothiaselenazolone 1,1-Dioxides

Krystian Kloc[a] and Jacek Mlochowski*[a]

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A convenient method for the synthesis of 2,2′-diselenobis(benzenesulfonamides) **4** and 2-substituted 1,3,2-benzothiaselenazole 1,1-dioxides **2**, has been elaborated. It is based on the conversion of 2-aminobenzenesulfonic acid into bis[2-(chlorosulfonyl)phenyl] diselenide (**6**), and reaction with ammonia or primary amines to give the sulfonamides **4**. Finally, cyclization of these sulfonamides by oxidation with benzoyl peroxide or by treatment of their sodium or potassium salt with elemental bromine produces 1,3,2-thiaselenazole 1,1-dioxides **2**.

Introduction

Benzisoselenazol-3(2*H*)-ones **1**, in particular ebselen (**1**, R = Ph), and the related 2,2′-diselenobis(benzenecarboxamides) **3** [also named bis(2-carbamoylphenyl) diselenides] are biomimetics of glutathione peroxidase. As such, they act as biological response modifiers, mainly as anti-inflammatory agents, and are therefore objects of current interest for organic chemists and medicinal biologists.[1][2] In our previous works, some of these compounds were reported as immunostimulants and virucides. They exhibited modest activity as inducers of many different cytokines such as interferons (mainly IFN-γ), tumor necrosis factor (TNF-α), and interleukines (IL-2, IL-4), and other factors in human peripheral blood leukocyte cultures.[3−7] Moreover, some of them exhibited activity as inhibitors of endothelial nitric oxide synthase (ce NOS).[6,8,9]

Expecting that replacement of the carboxamide group in compounds **1** and **3** by a sulfonamide group should result in increase of their biological activity, we designed compounds **2** and **4** as new potential immunostimulants and virucides (Scheme 1). In this paper we report a general method for the synthesis of 2,2′-diselenobis(benzenesulfonamides) **4** and their conversion into 1,3,2-benzothiaselenazole 1,1-dioxides **2** having a unique heterocyclic system with the selenium, sulfur and nitrogen atoms in the same ring. Although the synthesis of the first two representatives of compounds **2** [R = CH_3, $C(CH_3)_3$], obtained earlier in our laboratory, have already been reported[10,11] the problem of a general synthesis of different 2-substituted 1,3,2-benzisothiaselenazole 1,1-dioxides has not yet been resolved.

1 Z = CO
2 Z = SO_2
3 Z = CO
4 Z = SO_2

Scheme 1

Results and Discussion

The key substrate for the synthesis of 2,2′-diselenobis(benzenesulfonamides) **4** was bis[2-(chlorosulfonyl)phenyl] diselenide (**6**). It was obtained, in a total yield of 42% from sodium 2-aminobenzenesulfonate (**5**) in a four-step synthesis involving diazotization of **5** and reaction of the diazonium salt with potassium selenocyanate. It resulted in the formation of potassium 2-(cyanoseleno)benzenesulfonate which, when treated with aqueous potassium hydroxide, gave bis(2-sulfonylphenyl) diselenide which was then converted into sulfonyl chloride **6** by heating with phosphorus pentachloride. The details of the synthetic procedure have been described in ref.[10]

Bis[2-(chlorosulfonyl)phenyl] diselenide (**6**) thus obtained was treated with ammonia or primary aliphatic or aromatic amines to give 2,2′-diselenobis(benzenesulfonamides) **4a**−**k** in 74−98% yield (Scheme 2). This procedure, although involving five steps, seems to be more convenient and versatile than the recently elaborated synthesis of **4** based on direct lithiation and diselenenylation of phenylsulfonamides which is limited only to sulfonamides **4** having an unsubstituted phenyl or alkyl group[11] in the sulfamoyl moiety.

Seeking for a convenient method for the synthesis of 1,3,2-benzothiaselenazole 1,1-dioxides **2**, we tested different reactions leading to compound **2d**, presented in Scheme 3. Although the simplest way seemed to be direct cyclocondensation of a primary amine with 2-(chloroseleno)benzenesulfonyl chloride, the reaction could not be carried out because of the instability of the reagent.[10] A more stable reagent was 2-(bromoseleno)benzenesulfonyl chloride (**7**),

[a] Institute of Organic Chemistry, Biochemistry and Biotechnology, Wroclaw University of Technology,
Wyb. Wyspianskiego 27, PL-50 370, Wroclaw, Poland
Fax: (internat.) + 48-71/3284064
E-mail: Mlochowski@kchf.ch.pwr.wroc.pl

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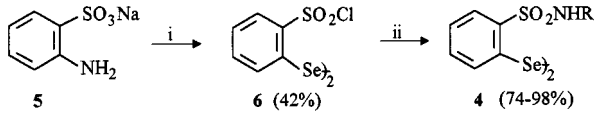


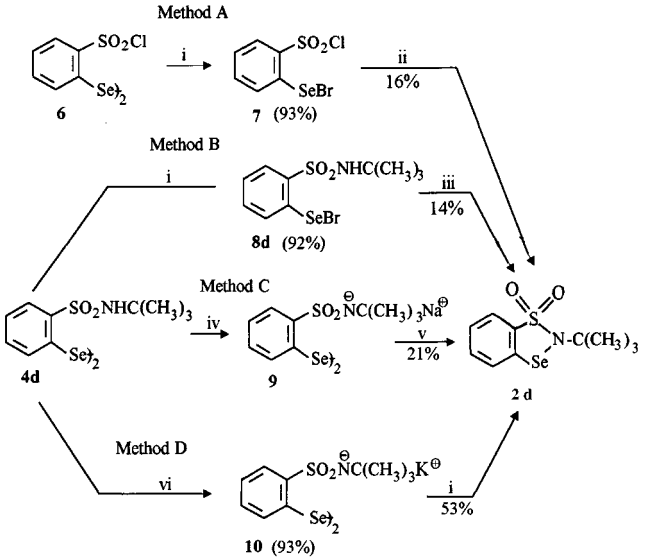
4	R	4	R
a	H	g	4-CH_3C_6H
b	CH_3	h	4-ClC_6H_4
c	n-C_3H_7	i	4-$CH_3OC_6H_4$
d	$C(CH_3)_3$	j	4-$HOOCC_6H_4$
e	cyclo-C_6H_{11}	k	2-pyridyl
f	C_6H_5		

Scheme 2. (i) 1. $NaNO_2$, H_2SO_4, −10°C; 2. KSeCN, H_2O, 0°C; 3. KOH, H_2O; 4. PCl_5, 150°C. − (ii) RNH_2, CH_2Cl_2 or pyridine, −10° to 20°C

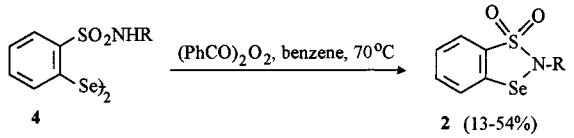
obtained from sulfonyl chloride by treatment with elemental bromine. Compound **7** was treated with *tert*-butylamine to give **2d** (Method A). The second method which led to **2d** (Method B) was based on the conversion of 2,2′-diselenobis(*N*-*tert*-butylbenzenesulfonamide) (**4d**) into 2-(bromoseleno)benzenesulfonamide (**8d**) followed by elimination of hydrogen bromide using triethylamine as a base. Treatment of other (bromoseleno)benzenesulfonamides **8a**, **b**, **j**, **k** with triethylamine, however, gave only the starting diselenides **4a**, **b**, **j**, **k**. Another approach (Method C) was based on the conversion of **4d** into sodium salt **9** and its direct cyclization (without isolation of **9**) into **2d** using elemental bromine.

Although Methods A−C led to the desired product **2d**, its yield did not exceed 21%, and the product was accompanied by substantial amounts (42−62%) of starting diselenide **4d**. More efficient was a two-step reaction (Method D) which involved conversion of **4d** into potassium salt **10** and subsequent ring closure with elemental bromine. In this way, the corresponding products **2d** and **2i** were obtained in 49% and 27% yields from **4d** and **4i**, respectively. Unfortunately, the scope of this method was limited to these two examples, and from other salts, obtained from **4a**−**c** and **4d**−**h**, only the starting substrates **4** were recovered.

The recently reported generation of the amidyl radical from 2-(triphenylstannylseleno)benzamides with benzoyl peroxide[12] prompted us to carry out the oxidative cyclization of 2,2′-diselenobis(benzenesulfonamides) **4** to 1,3,2-benzisoselenazole 1,1-dioxides **2** using the same reagent as an oxidant (Scheme 4). The desired products **2b**−**h**, among them **2f** which is a close analogue of ebselen, were obtained in 13−49% yield. They were accompanied by the diselenides **4b**−**h** which could be recovered in 24−54% yields. The oxidative cyclization of **4** presented seems to be the most general method for the synthesis of **2**, although it is limited by the solubility of the substrate in benzene and the susceptibility towards side-oxidative transformations. Thus, insoluble **4h** gave product **2h** in 13% yield only and for **4a**, **j**, **k** no formation of **2a**, **j**, **k** was observed. The reaction of **4i** was more complex, most probably because of the sensitivity of its aromatic moiety towards oxidation, and only a tar-like mixture of several unidentified products was obtained.



Scheme 3. (i) Br_2, CCl_4, −10 to 20°C. − (ii) $H_2NC(CH_3)_3$, CH_2Cl_2, −10°C. − (iii) $(C_2H_5)_3N$, CCl_4, −10°C. − (iv) NaH, CH_2Cl_2, 20°C. − (v) Br_2, CH_2Cl_2, −10 to 20°C. − (vi) *t*BuOK, *t*BuOH, reflux



2, 4	R	2, 4	R
b	CH_3	f	C_6H_5
c	n-C_3H_7	g	4-$CH_3C_6H_4$
d	$C(CH_3)_3$	h	4-ClC_6H_4
e	cyclo-C_6H_{11}		

Scheme 4

Experimental Section

General: Melting points: Digital Melting Point Apparatus Electrothermal IA 9100. − ^1H NMR: Bruker 300-MHz spectrometer. − IR (KBr pellets): Perkin-Elmer 2000 FT. − All starting materials were purchased from Aldrich Chem. Co. and Fluka.

Synthesis of 2,2′-Diselenobis(benzenesulfonamides) 4a−k. − General Procedure: A solution of amine (50 mmol) in dry dichloromethane (25 mL) was added dropwise over a period of 1 h to a stirred and cooled (ice/salt bath) solution of sulfonyl chloride **6** (2.55 g, 5 mmol) (obtained according to the procedure reported in ref.[10]) in dry dichloromethane (50 mL). The gaseous substrate (ammonia, methylamine) was passed through the reaction mixture until all of **6** was exhausted (ca. 15 min). After 3 h, during which the mixture was allowed to warm to room temperature, the solvent and excess of amine were removed in vacuo. From the residue, amine hydrochloride was washed off by stirring with water over a period of 6 h and the product **4a**−**d** was filtered off and recrystallized from methanol. When a low-volatility amine (cyclohexylamine, arylamine) (11 mmol) was used as a substrate, it was dissolved in dry pyridine (25 mL), and to this stirred and cooled (ice bath) solution, sulfonyl chloride **6** (2.55 g, 5 mmol) was added portionwise over a period of 30 min. After 3 h (**4e**−**j**) or 20 h (**4k**), during which the reaction mixture was allowed to warm to room

temperature, the pyridine was evaporated in vacuo. To the residue, water (100 mL) (for **4k**) or 5% hydrochloric acid (for **4e**−**i**) was added. It was then stirred for 6 h, the product filtered off, dried in air, dissolved in chloroform (**4e**, **f**, **g**, **i**), acetone (**4h**) or methanol (**4j**) and filtered through silica gel. The solvent was evaporated from the filtrate in vacuo and the residue was recrystallized from chloroform (**4h**), chloroform/hexane (1:1) (**4e**, **f**, **g**, **i**) or water/acetone (5:1) (**4i**) to give a pure product which was dried in air (**4e**−**i**) or at a temperature of 120°C (**4j**). For isolation of **4k**, the residue after pyridine evaporation was suspended in satd. aq. sodium hydrogen carbonate (80 mL) and stirred until carbon dioxide evolved (ca. 5 h). The product was filtered off, washed with water, methanol and recrystallized from DMSO/methanol.

2,2′-Diselenobis(benzenesulfonamide) (4a): Pale yellow powder. Yield 2.12 g (90%), m.p. 253−255°C (decomp.). − ^{1}H NMR (DMSO, TMS): δ = 7.42−7.50 (m, 4 H, ArH); 7.75 (s, 4 H, NH_2); 7.78−7.84 (m, 2 H, ArH); 7.86−7.91 (m, 2 H, ArH). − IR: $\tilde{\nu}$ = 1153 cm^{-1}, 1328 (SO_2), 3250, 3363 (NH_2). − $C_{12}H_{12}N_2O_4S_2Se_2$ (470.28): calcd. C 30.65, H 2.57, N 5.96, S 13.63; found C 30.82, H 2.85, N 5.78, S 13.40.

2,2′-Diselenobis(*N*-methylbenzenesulfonamide) (4b): Yellow prisms. Yield 2.78 g (74%), m.p. 185−187°C (ref.[10] 185−187°C).

2,2′-Diselenobis(*N*-propylbenzenesulfonamide) (4c): Yellow prisms. Yield 2.56 g (92%), m.p. 130−132°C (ref.[11] 125−128°C).

2,2′-Diselenobis(*N*-*tert*-butylbenzenesulfonamide) (4d): Yellow prisms. Yield 2.68 g (92%), m.p. 208−209°C (ref.[11] 207−209°C).

2,2′-Diselenobis(*N*-cyclohexylbenzenesulfonamide) (4e): Yellow prisms. Yield 2.70 g (85%), m.p. 210−212°C (ref.[11] 210−212°C).

2,2′-Diselenobis(*N*-phenylbenzenesulfonamide) (4f): Yellow needles. Yield 2.55 g (82%), m.p. 155−157°C (ref.[11] 154−155°C).

2,2′-Diselenobis[*N*-(4-methylphenyl)benzenesulfonamide] (4g): Yellow needles 3.19 g (98%), m.p. 175−177°C. − ^{1}H NMR ($CDCl_3$, TMS): δ = 2.25 (s, 6 H, CH_3); 6.86 (d, 4 H, *J* = 8.4 Hz, ArH); 6.97 (s, 2 H, NH); 7.01 (d, 4 H, *J* = 47.4 Hz, ArH); 7.24 (dt, 2 H, *J* = 7.5 and 1.2 Hz, ArH); 7.31 (dt, 2 H, *J* = 7.5 and 1.7 Hz, ArH); 7.76 (dd, 2 H, *J* = 7.7 and 1.6 Hz, ArH); 7.82 (dd, 2 H, *J* = 7.7 and 1.7 Hz, ArH). − IR: $\tilde{\nu}$ = 1153 cm^{-1}, 1331 (SO_2), 3298 (NH). − $C_{26}H_{24}N_2O_4S_2Se_2$ (650.51): calcd. C 48.00, H 3.72, N 4.39, S 9.86; found C 47.8, H 3.89, N 4.60, S 9.70.

2,2′-Diselenobis[*N*-(4-chlorophenyl)benzenesulfonamide] (4h): Yellow needles 3.18 g (92%), m.p. 184−186°C. − ^{1}H NMR ($CDCl_3$, TMS): δ = 6.93 (d, 4 H, *J* = 6.7 Hz, ArH); 7.08 (s, 2 H, NH); 7.17 (d, 4 H, *J* = 6.7 Hz, ArH); 7.30−7.38 (m, 4 H, ArH); 7.78−7.82 (m, 4 H, ArH). − IR: $\tilde{\nu}$ = 1154 cm^{-1}, 1328 (SO_2), 3294 (NH). − $C_{24}H_{18}Cl_2N_2O_4S_2Se_2$ (691.35): calcd. C 41.69, H 2.62, Cl 10.27, N 4.05, S 9.27; found C 41.94, H 2.69, Cl 10.50, N 3.86, S 9.0.

2,2′-Diselenobis[*N*-(4-methoxyphenyl)benzenesulfonamide] (4i): Yellow prisms 3.17 g (93%), m.p. 183−185°C. − ^{1}H NMR ($CDCl_3$, TMS): δ = 3.73 (s, 6 H, CH_3); 6.71 (d, 4 H, *J* = 9.0 Hz, ArH); 6.90 (d, 4 H, *J* = 9.0 Hz, ArH); 6.93 (s, 2 H, NH); 7.24 (dt, 2 H, *J* = 7.5 and 1.1 Hz, ArH); 7.35 (dt, 2 H, *J* = 7.6 and 1.5 Hz, ArH); 7.70 (dd, 2 H, *J* = 7.7 and 1.5 Hz, ArH); 7.84 (dd, 2 H, *J* = 7.9 and 1.7 Hz, ArH). − IR: $\tilde{\nu}$ = 1154 cm^{-1}, 1332 (SO_2), 3290 (NH). − $C_{26}H_{24}N_2O_6S_2Se_2$ (682.51): calcd. C 45.75, H 3.54, N 4.10, S 9.39; found C 46.00, H 3.64, N 4.36, S 9.32.

2,2′-Diselenobis[*N*-(4-carboxyphenyl)benzenesulfonamide] (4j): Pale yellow powder 3.33 g (94%), m.p. 196−199°C. − ^{1}H NMR (DMSO, TMS): δ = 7.22 (d, 4 H, *J* = 8.7 Hz, ArH); 7.31 (dt, 2 H, *J* = 7.7 and 14.3 Hz, ArH); 7.41 (dt, 2 H, *J* = 7.5 and 1.0, ArH); 7.64 (dd, 2 H, *J* = 7.9 and 0.6 Hz, ArH); 7.83 (d, 4 H, *J* = 8.7 Hz, ArH); 7.94 (dd, 2 H, *J* = 7.8 and 1.2 Hz, ArH); 11.26 (s, 2 H, NH); 12.77 (s, 2 H, COOH). − IR: $\tilde{\nu}$ = 1158 cm^{-1}, 1337 (SO_2), 1683 (CO), 2540−3060 (OH), 3244 (NH). − $C_{26}H_{20}N_2O_8S_2Se_2$ (710.48): calcd. C 43.95, H 2.84, N 3.94, S 9.02; found C 43.71, H 3.11, N 4.10, S 8.70.

2,2′-Diselenobis[*N*-(2-pyridyl)benzenesulfonamide] (4k): Yellow powder 2.68 g (86%), m.p. 280−281°C. − ^{1}H NMR (DMSO, TMS): δ = 6.84 (t, 2 H, *J* = 6.5 Hz, PyH); 7.19 (d, 2 H, *J* = 8.9 Hz, PyH); 7.25 (t, 2 H, *J* = 4.5 Hz, ArH); 7.34 (t, 2 H, *J* = 7.4, ArH); 7.62 (d, 2 H, *J* = 7.8 Hz, ArH); 7.78−7.83 (m, 2 H, PyH); 7.91−7.96 (m, 4 H, ArH and PyH); 12.62 (s, 1 H, NH). − IR: $\tilde{\nu}$ = 1142 cm^{-1}, 1383 (SO_2), 3221 (NH). − $C_{22}H_{18}N_4O_4S_2Se_2$ (624.43): calcd. C 42.31, H 2.90, N 8.97, S 10.27; found C 42.02, H 3.20, N 8.52, S 10.61.

2-(Bromoseleno)benzenesulfonyl Chloride (7): A solution of bromine (1.34 g, 8.4 mmol) in dry carbon tetrachloride (30 mL) was added dropwise to a suspension of chloride **6** (4.07 g, 8 mmol) in carbon tetrachloride (30 mL). The mixture was vigorously stirred and cooled on an ice/salt bath for 30 min. After 3 h, during which the mixture was allowed to warm to room temperature, the solvent was evaporated in vacuo. The residue recrystallized from hexane giving compound **7** as red prisms (5.0 g, 93%), m.p. 40−41°C. − ^{1}H NMR ($CDCl_3$, TMS): δ = 7.51 (dt, 1 H, *J* = 7.6 and 1.0 Hz, ArH); 7.70 (dt, 1 H, *J* = 7.8 and 1.4 Hz, ArH); 8.03 (dd, 1 H, *J* = 7.6 and 1.4 Hz, ArH); 8.05 (dd, 1 H, *J* = 8.1 and 1.0 Hz, ArH). − IR: $\tilde{\nu}$ = 1172 cm^{-1}, 1364 (SO_2). − Elemental analyses gave irreproducible results.

Synthesis of the 2-(Bromoseleno)benzenesulfonamides 8a, b, d, j, k. − General Procedure: To a stirred suspension of **4** (1.0 mmol) in dry carbon tetrachloride (25 mL) cooled with an ice/salt bath, a solution of bromine in the same solvent (10 mL) was added dropwise during 30 min. During the following 3 h (**8b**,**d**) or 24 h (**8a**, **j**, **k**) the mixture was allowed to warm to room temperature. For **8b**, **d** the solvent was evaporated in vacuo from the water bath (30−35°C) and the crude product was recrystallized from hexane. The products **8a**, **j**, **k** were filtered off from the reaction mixture, washed with carbon tetrachloride and dried in air. The compounds **8a**, **b**, **d**, **j**, **k** were identified by IR and ^{1}H-NMR spectroscopy. Elemental analyses gave irreproducible results.

2-(Bromoseleno)benzenesulfonamide (8a): Orange-red powder. Yield 0.59 g (94%), m.p. 188−190°C (decomp.). − ^{1}H NMR (DMSO, TMS): δ = 7.44 (t, 1 H, *J* = 6.6 Hz, ArH); 7.59 (t, 1 H, *J* = 7.6 Hz, ArH); 7.69 (d, 1 H, *J* = 8.9 Hz, ArH); 8.09 (d, 1 H, *J* = 7.9 Hz, ArH); 9.50 (br. s, 2 H, NH_2). − IR: $\tilde{\nu}$ = 1165 cm^{-1}, 1329 (SO_2), 3242, 3353 (NH_2).

2-(Bromoseleno)-*N*-methylbenzenesulfonamide (8b): Orange-red needles. Yield 0.62 g (94%), m.p. 91−93°C (decomp.). − ^{1}H NMR ($CDCl_3$, TMS): δ = 2.69 (d, 3 H, *J* = 5.4 Hz, CH_3); 4.87 (br. s, 1 H, NH); 7.43 (t, 1 H, *J* = 7.6 Hz, ArH); 7.59 (td, 1 H, *J* = 7.6 Hz ArH); 7.59 (td, 1 H, *J* = 7.7 and 1.4 Hz, ArH); 7.81 (dd, 1 H, *J* = 7.8 and 1.3 Hz, ArH); 8.00 (d, 1 H, *J* = 8.0 Hz, ArH). − IR: $\tilde{\nu}$ = 1154 cm^{-1}, 1320 (SO_2), 3288 (NH).

2-(Bromoseleno)-*N*-*tert*-butylbenzenesulfonamide (8d): Reddish-brown needles. Yield 0.68 g (92%), m.p. 90−91°C (decomp.). − ^{1}H NMR ($CDCl_3$, TMS): δ = 1.25 (s, 9 H, CH_3); 5.00 (s, 1 H, NH); 7.40 (dt, 1 H, *J* = 7.6 and 1.1 Hz, ArH); 7.54 (dt, 1 H, *J* = 7.7 and 1.5 Hz, ArH); 7.85 (dd, 1 H, *J* = 7.7 and 1.5 Hz, ArH); 7.97 (dd, 1 H, *J* = 8.0 and 1.0 Hz, ArH). − IR: $\tilde{\nu}$ = 1150 cm^{-1}, 1290 (SO_2), 2972 (CH), 3297 (NH).

2-(Bromoseleno)-*N*-(4-carboxyphenyl)benzenesulfonamide (8j): Reddish-brown needles. Yield 0.83 g (96%), m.p. 203−204°C (decomp.). − ^{1}H NMR (DMSO, TMS): δ = 7.27 (d, 2 H, *J* = 8.7 Hz, ArH); 7.50 (dt, 1 H, *J* = 7.5 and 0.8 Hz, ArH); 7.64 (dt, 1 H, *J* = 7.7 and 1.2 Hz, ArH); 7.73 (dd, 1 H, *J* = 7.7 and 1.3 Hz, ArH); 7.87 (d, *J* = 6.8 Hz, ArH); 8.32 (d, 1 H, *J* = 7.9 Hz, ArH); 9.99 (br. s, 2 H, NH, COOH). − IR: $\tilde{\nu}$ = 1157 cm^{-1}, 1328 (SO_2), 1680 (CO), 2548−3010 (OH), 3267 (NH).

2-(Bromoseleno)-*N*-(2-pyridyl)benzenesulfonamide (8k): Orange-red powder. Yield 0.69 g (88%), m.p. 213−214 (decomp.). − ^{1}H NMR ($CDCl_3$/DMSO, TMS): δ = 6.84−6.89 (m, 1 H, PyH); 7.36−7.41 (m, 1 H, ArH); 7.46−7.52 (m, 2 H, ArH, PyH); 7.76−7.91 (m, 3 H, ArH, PyH); 13.1 (br. s, 1 H, NH); 8.05 (dd, 1 H, *J* = 8.1 and 1.1 Hz, ArH). − IR: $\tilde{\nu}$ = 1152 cm^{-1}, 1344 (SO_2), 3224 (NH).

Synthesis of 2-*tert*-Butyl-1,3,2-benzothiaselenazole 1,1-Dioxide (2d). − Method A: A solution of compound **7** (0.502 g, 1.5 mmol) in dry dichloromethane (10 mL) was added dropwise over 1 h to a stirred and cooled (ice/salt bath) solution of *tert*-butylamine (0.33 g, 4.5 mmol) in dry dichloromethane (10 mL). After additional 30 min, the precipitated solid was filtered off, the solvent was evaporated from the filtrate in vacuo, and from the residue **2d** was separated by the silica gel chromatography (dichloromethane), and recrystallized from carbon tetrachloride. Yield 0.069 g (16%). The next eluted fraction was **4c** (0.182 g, 42%). − **Method B:** A solution of compound **8d** (0.722 g, 2.0 mmol) in dry carbon tetrachloride (20 mL) was added dropwise to a solution of triethylamine (0.223 g, 2.2 mmol) in the same solvent (20 mL), cooled with an ice/salt bath, over a period of 30 min. During the following 3 h, the mixture was allowed to warm to room temperature. From the reaction mixture, worked up as outlined in Method A, **2d** (0.083 g, 14%) and **4d** (0.249 g, 50%) were isolated. − **Method C:** A solution of compound **4d** (1.456 g, 2.5 mmol) in dry dichloromethane (25 mL) was added at room temperature to a suspension of oil-free sodium hydride (0.132 g, 5.5 mmol) in anhydrous dichloromethane (25 mL), and the reaction was continued for 5 d, until the evolution of hydrogen had ceased. To this mixture, cooled with an ice/salt bath, a solution of bromine (0.440 g, 2.75 mmol) in dichloromethane (25 mL) was added dropwise. During the following 18 h the mixture was allowed to warm to room temperature and then it was worked up as in Method A to give **2d** (0.307 g, 21%) and **4d** (0.901 g, 62%). − **Method D:** A 100-mL round-bottom flask containing a solution of potassium *tert*-butoxide (0.294 g, 2.62 mmol) in dry *tert*-butyl alcohol (50 mL), was fitted with a pressure-equalising dropping funnel, containing **4d** (0.872 g, 1.25 mmol). The funnel was stoppered with a moisture-protected condenser and the solution in the flask was magnetically stirred and refluxed until all **4d** had dissolved (ca. 2 h). Heating was then continued for 1 h. After the reaction had finished, *tert*-butyl alcohol was decanted and the rest of it was removed in vacuo to give **10** (0.763 g, 1.16 mmol, 93%). The product was suspended in dry carbon tetrachloride (60 mL) and to this suspension, stirred and cooled on an ice/salt bath, a solution of bromine (0.203 g, 1.27 mmol) in dry carbon tetrachloride (20 mL) was added dropwise during 1.5 h. During the following 18 h the mixture was allowed to warm to room temperature. Then it was heated and potassium bromide was filtered off and washed with hot carbon tetrachloride. The solvent was removed from the filtrate under reduced pressure to yield pure **2d** (0.387 g, 53%).

General Procedure for the Synthesis of 1,3,2-Benzothiaselenazole 1,1-Dioxides 2b−h by Oxidative Cyclization of 4b−h: A mixture of the appropriate compound **4** (1.0 mmol), benzoyl peroxide (0.266 g, 1.1 mmol) and dry benzene (30 mL) was stirred and heated to 70°C for 24 h. After the reaction had finished, the benzene was evaporated in vacuo and the residue was separated by silica gel chromatography (dichloromethane) to give **2**, which was recrystallized from carbon tetrachloride (**2b**−**d**), methanol (**2g**, **h**), benzene (**2f**) or cyclohexane/benzene (1:1) (**2e**). The next eluted fraction was compound **4** (**4b**, 26%; **4c**, 33%; **4d**, 32%; **4e**, 42%; **4f**, 24%; **4g**, 36%; **4h**, 54%).

2-Methyl-1,3,2-benzothiaselenazole 1,1-Dioxide (2b): White needles. Yield 0.262 g (54%), m.p. 98−100°C (ref.[10] 98−100°C).

2-Propyl-1,3,2-benzothiaselenazole 1,1-Dioxide (2c): Colourless prisms. Yield 0.25 g (46%), m.p. 84−86°C. − ^{1}H NMR ($CDCl_3$, TMS): δ = 0.96 (t, 3 H, *J* = 7.3 Hz, CH_3); 1.67 (sext, 2 H, *J* = 7.3 Hz, CH_2CH_3); 3.30 (t, 2 H, *J* = 7.3 Hz, NCH_2), 7.44 (dt, 1 H, *J* = 7.4 and 1 Hz, ArH); 7.49 (d, 1 H, *J* = 7.6 Hz, ArH); 7.58 (dt, 1 H, *J* = 7.6 and 1.2 Hz, ArH); 7.76 (d, 1 H, *J* = 7.5 Hz, ArH). − IR: $\tilde{\nu}$ = 1600 cm^{-1}, 1320 (SO_2). − $C_9H_{11}NO_2SSe$ (276.21): calcd. C 39.19, H 4.01, N 5.07, S 11.61; found C 39.40, H 4.21, N 4.80, S 11.45.

2-*tert*-Butyl-1,3,2-benzothiaselenazole 1,1-Dioxide (2d): Colourless needles. Yield 0.35 g (61%), m.p. 112.5−115°C (ref.[11] 113−115°C).

2-Cyclohexyl-1,3,2-benzothiaselenazole 1,1-Dioxide (2e): Colourless flakes. Yield 0.23 g (36%), m.p. 205−206°C (decomp.). − ^{1}H NMR ($CDCl_3$, TMS): δ = 1.23−1.34 (m, 4 H, CH_2); 1.61−1.72 (m, 6 H, CH_2); 3.73−3.82 (m, 1 H, CH); 7.38−7.43 (m, 1 H, ArH); 7.48 (d, 1 H, *J* = 6.9 Hz, ArH); 7.51−7.57 (m, 1 H, ArH); 7.71 (d, 1 H, *J* = 7.4 Hz, ArH). − IR: $\tilde{\nu}$ = 1170 cm^{-1}, 1329 (SO_2), 2853, 2926 (CH). − $C_{12}H_{15}NO_2SSe$ (316.27): calcd. C 45.57, H 4.78, N 4.43, S 10.14; found C 45.71, H 4.58, N 4.70, S 10.07.

2-Phenyl-1,3,2-benzothiaselenazole 1,1-Dioxide (2f): Colourless needles. Yield 0.19 g (31%), m.p. 192−194°C (decomp.). − ^{1}H NMR ($CDCl_3$, TMS): δ = 7.18−7.30 (m, 5 H, ArH); 7.48 (t, 1 H, *J* = 7.2 Hz ArH); 7.60 (d, 1 H, *J* = 7.2 Hz, ArH); 7.64 (t, 1 H, *J* = 7.4 Hz, ArH), 7.78 (d, 1 H, *J* = 7.8 Hz, ArH). − IR: $\tilde{\nu}$ = 1170 cm^{-1}, 1339 (SO_2). − $C_{12}H_9NO_2SSe$ (310.22): calcd. C 46.46, H 2.92, N 4.52, S 10.33; found C 46.70, H 3.19, N 4.30, S 10.50.

2-(4-Methylphenyl)-1,3,2-benzothiaselenazole 1,1-Dioxide (2g): Pale yellow needles. Yield 0.17 g (27%), m.p. 194−195°C (decomp.). − ^{1}H NMR ($CDCl_3$, TMS): δ = 2.31 (s, 3 H, CH_3), 7.06−7.12 (m, 4 H, ArH); 7.44−7.49 (m, 1 H, ArH), 7.58−7.67 (m, 2 H, ArH); 7.75−7.78 (m, 1 H, ArH). − IR: $\tilde{\nu}$ = 1171 cm^{-1}, 1346 (SO_2). − $C_{13}H_{11}NO_2SSe$ (324.25): calcd. C 48.15, H 3.42, N 4.32, S 9.89; found C 48.43, H 3.57, N 4.53, S 9.80.

2-(4-Chlorophenyl)-1,3,2-benzothiaselenazole 1,1-Dioxide (2h): Pale yellow prisms. Yield 0.09 g (13%), m.p. 159−160°C (decomp.). − ^{1}H NMR ($CDCl_3$, TMS): δ = 7.15 (d, 2 H, *J* = 8.9 Hz, ArH); 7.25 (d, 2 H, *J* = 8.9 Hz, ArH); 7.49 (dt, 1 H, *J* = 7.3 and 1.4 Hz, ArH); 7.61 (dd, 1 H, *J* = 7.8 and 1.5 Hz, ArH); 7.67 (dt, 1 H, *J* = 7.5 and 1.2 Hz, ArH); 7.76 (dd, 1 H, *J* = 8.2 and 0.8 Hz, ArH). − IR: $\tilde{\nu}$ = 1160 cm^{-1}, 1334 (SO_2). − $C_{12}H_8ClNO_2SSe$ (344.67): calcd. 41.81, H 2.34, N 4.06, S 9.30, Cl 10.28; found C 41.62, H 2.29, N 4.16, S 9.49, Cl 10.14.

2-(4-Methoxyphenyl)-1,3,2-benzothiaselenazole 1,1-Dioxide (2i), Obtained by Method D: Yellow plates. Yield 0.23 g (27%), m.p. 152−153°C (decomp.). − ^{1}H NMR ($CDCl_3$, TMS): δ = 3.77 (s, 3 H, OCH_3); 6.78 (d, 2 H, *J* = 8.9 Hz, ArH); 7.13 (d, 2 H, *J* = 8.9 Hz, ArH); 7.47 (t, 1 H, *J* = 7.4 Hz, ArH); 7.59 (d, 1 H, *J* = 7.5 Hz, ArH); 7.65 (t, 1 H, *J* = 7.4 Hz, ArH); 7.78 (d, 1 H, *J* = 7.7 Hz, ArH). − IR: $\tilde{\nu}$ = 1176 cm^{-1}, 1342 (SO_2). − $C_{13}H_{11}NO_3SSe$ (340.25): calcd. C 45.89, H 3.26, N 4.12, S 9.42; found C 45.60, H 3.24, N 4.06, S 9.00.

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