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New heterocyclic selenenamides: 1,2,4-benzoselenadiazin-3(4*H*)-ones and 1,3,2-benzodiselenazoles

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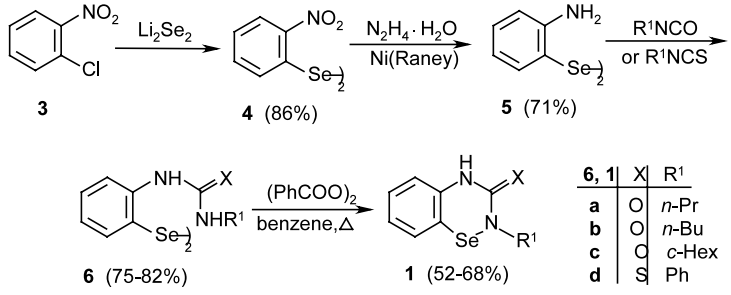
Abstract—Two groups of selenium-containing heterocycles having new, unique 1,2,4-benzoselenadiazine and 1,3,2-diselenazole ring systems with an endocyclic selenenamide C–N moiety are presented. The first type was obtained by oxidative cyclization of 2,2′-diselenobis(phenylureas) and the second type by the reaction of 1,2-di(bromoseleno)benzene with primary amines.

Selenium-containing heterocycles, particularly those having the endocyclic selenenamide Se–N moiety and related diaryl diselenides play an important role in medicinal biology as biological response modifiers.[1] Some of them, particularly 2-phenyl-1,2-benzisoselenazol-3(2*H*)-one (ebselen) its derivatives and analogues, were found as glutathione peroxidase mimics, anti-inflammatory, antiatherosclerotic, anticancer, antimicrobial and antiviral agents as well as immunostimulants, cytokine inducers and nitric oxide synthase inhibitors.[2] Moreover, the ebselen and camphor derived selenenamide, and bis[2-(phenylcarbamoyl)phenyl] diselenides were used as efficient oxygen-transfer catalysts for hydroperoxide oxidation the different groups of organic compounds such as sulfides, thiols, ketazines, aldazines, oximes, *N*,*N*-dimethylhydrazones, aldehydes and alkylarenes.[2h,3]

In this work, we present a simple approach for the synthesis of two different groups of heterocycles having new selenium and nitrogen-containing six- and five-membered 1,2,4-benzoselenadiazine and 1,3,2-benzodiselenazole ring systems.

2-Substituted 1,2,4-benzoxaselenadiazin-3(4*H*)-ones (**1a**–**c**) were synthesized starting from 1-chloro-2-nitrobenzene **3**. Compound **3** was treated with dilithium diselenide in an aprotic medium according to the procedure reported earlier,[4] to give bis(2-nitrophenyl) diselenide **4** which was reduced with hydrazine, in the presence of catalytic Ni (Raney) to afford bis(2-aminophenyl) diselenide **5**.[5,6] Both amino groups were converted to the corresponding aminocarbamoyl by treatment of **5** with isocyanates.[7] The 2,2′-diselenobis(phenylureas) (**6a**–**c**) thus formed were oxidatively



Scheme 1.

Keywords: organoselenium compounds; benzoselenadiazinone; benzoselenadiazinthiones; benzodiselenazoles; selenenamides.

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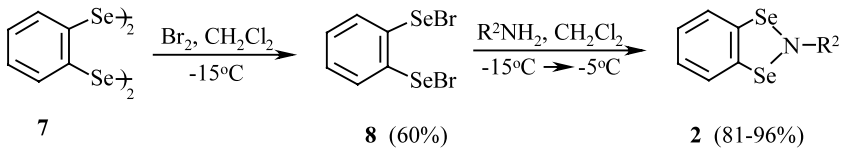

7 **8** (60%) **2** (81-96%)

R^2: *n*-Pr (**2a**). *n*-Bu (**2b**), *i*-Bu (**2c**), *t-Bu (***2d**), *sec*-Bu (**2e**)

Scheme 2.

cyclized to the final products **1a–c** (Scheme 1).[8] A comparison of the ^{1}H NMR spectra of substrates **6** and products **1** indicated that only one pair of NH protons remained (primary observed at ca. 6.7 ppm), and that the multiplicity of the NCH proton signal in the spectra of compounds having *N*-alkyl substituents (**1a–c**) was decreased. This evidence confirmed that oxidative elimination of a hydrogen atom and ring closure had occurred. Benzoyl peroxide was used as the oxidant of choice since it had successfully been used earlier for Se–N bond formation in other heterocyclic ring systems.[9] Nevertheless, it was observed that the reaction was limited to diselenides of type **6** which are soluble in benzene or toluene. 2,2′-Diselenobis(phenylureas) having an aryl substituent (phenyl, 4-nitrophenyl, 3-chlorophenyl, 3,4-dichlorophenyl) on the terminal nitrogen atom of the urea moiety were insoluble in these solvents and remained unreacted.

Replacement of the aminocarbamoyl group by an aminothiocarbamoyl group made 2,2′-diselenobis(phenylthiourea) **6d** soluble in benzene. Thus, compound **6d**, obtained from diselenide **5** and phenylisothiocyanate, was smoothly converted into the expected 2-phenyl-1,2,4-benzoxaselenadiazin-3(4*H*)-thione **1d** by oxidation with benzoyl peroxide. The lack of one pair of NH protons (primary observed in the ^{1}H NMR spectrum of the substrate **6d** at 8.33 ppm) supports the proposed cyclic structure of the product **1d**.

Starting from poly(bis-1,2-phenylene) diselenide **7**, prepared recently in our laboratory,[10] 2-substituted 1,3,2-benzodiselenazoles (**2a–e**) were synthesized. The diselenide **7**, brominated with elemental bromine, gave 1,2-di(bromoseleno)benzene **8**[11,12] which was subsequently treated with primary alkylamines to produce the desired heterocycles **2** (Scheme 2).[13] Their ^{1}H NMR spectra and elemental analyses support the proposed structures. The analogous reaction of **8** with aromatic amines (aniline, 4-nitroaniline) gave no positive results since the corresponding products **2** could not be isolated due to their instability.

Acknowledgements

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5. To a solution of diselenide **4** (18.0 g, 45 mmol) in propanol (150 ml) heated to 95°C, Raney nickel (ca. 10 g) was added and then hydrazine monohydrate (15 ml, 300 mmol) was added dropwise and the mixture was stirred for 3 h. The reaction was continued for an additional 2 h and the hot mixture was filtered. The solvent was evaporated in vacuo and the residue was recrystallized from ethanol. Compound **5**: yield 71%, bright orange-red prisms, mp 83.2°C (Ref. 6 83.5°C).
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7. The mixture of amine **5** (3.42 g, 10 mmol) and the corresponding isocyanate or isothiocyanate (30 mmol) was heated for 2–30 h at 80°C until it solidified. The excess of reagent was evaporated in vacuo and the crude product was recrystallized from toluene to give pure (**6a–d**). Compound **6a**: yield 81%, mp 174–175°C, yellow

prisms. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 0.88 (t, 6H, J=7.3 Hz, CH_3), 1.40–1.47 (m, 4H, CH_2), 2.99–3.31 (m, 4H, CH_2N), 6.76 (t, 2H, J=7.4 Hz, NH), 6.89 (t, 2H, J=7.5 Hz, ArH), 7.21 (t, 2H, J=7.5 Hz, ArH), 7.49 (d, 2H, J=8.0 Hz, ArH), 7.59 (d, 2H, J=8.0 Hz, ArH), 8.01 (s, 2H, ArNH). IR (KBr) 3306, 3097, 2958, 2931, 2872, 1639. Anal. calcd for $C_{20}H_{26}N_4O_2Se_2$: C, 46.86; H, 5.11; N, 10.94. Found: C, 46.99; H, 5.20; N, 11.12. Compound **6b**: yield 80%, mp 155–157°C, bright yellow prisms. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 0.87 (t, 6H, J=7.2 Hz, CH_3), 1.17–1.29 (m, 4H, CH_2), 1.39–1.49 (m, 4H, CH_2), 3.28 (m, 4H, CH_2N), 6.72 (t, 2H, J=7.4 Hz, NH), 6.97 (t, 4H, J=7.4 Hz, ArH), 7.21 (t, 2H, J=7.7 Hz, ArH), 7.40 (d, 2H, J=7.7 Hz, ArH), 8.01 (s, 2H, ArNH). IR (KBr) 3305, 3093, 2952, 2929, 2870, 1641. Anal. calcd for $C_{22}H_{30}N_4O_2Se_2$: C, 48.87; H, 5.60; N, 10.37%. Found: C, 49.01; H, 5.73; N, 10.58%. Compound **6c**: yield 75%, mp 210–211°C bright yellow prisms. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 0.98–1.56 (m, 12H, CH_2), 1.64–1.67 (m, 4H, CH_2), 1.79–1.82 (m, 4H, CH_2), 3.41–3.45 (m, 2H, CH), 6.72 (d, 2H, J=7.7 Hz, NH), 6.88 (t, 2H, J=7.2 Hz, ArH), 7.21 (t, 2H, J=7.2 Hz, ArH), 7.48 (d, 2H, J=7.2 Hz, ArH), 7.61 (d, 2H, J=7.7 Hz, ArH), 7.94 (s, 2H, ArNH). IR (KBr) 3322, 3083, 2952, 2929, 2852, 1643. Anal. calcd for $C_{26}H_{34}N_4O_2Se_2$: C, 52.68; H, 5.77; N, 9.46. Found: C, 52.35; H, 5.42; N, 9.55%. Compound **6d**: yield 82%, mp 121–122°C yellow prisms. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 6.94–6.99 (m, 4H, ArH), 7.23–7.30 (m, 6H, ArH), 7.45 (d, 4H, J=7.7 Hz, ArH), 7.55 (d, 2H, J=7.7 Hz, ArH), 7.70 (d, 2H, J=8.1 Hz, ArH), 8.33 (s, 2H, ArNH), 9.23 (s, 2H, ArNH). IR(KBr) 3451, 3179, 3118, 3047, 2935, 2856, 1624, 1558, 1450, 1241, 1220, 743, 699. Anal. calcd for $C_{26}H_{22}N_4S_2Se_2$: C, 50.98; H, 3.62; N, 9.14. Found: C, 51.14; H, 3.73; N, 9.21%.

8. A magnetically stirred solution of 2,2′-diselenobis(phenylurea) (**6a–c**) or 2,2′-diselenobis(phenylthiourea) (**6d**) (1 mmol) and benzoyl peroxide (1.1 mmol) in dry benzene (30 ml) was heated to 80°C for 20 h. After this period the solvent was evaporated in vacuo. The products **1** were isolated from the residue by column chromatography on silica gel using hexane–ethyl acetate (4:1) as eluent and recrystallized from toluene. Compound **1a**: yield 65%, mp 106–107°C, yellow prisms. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 0.81 (t, 3H, J=7.3 Hz, CH_3), 1.42–1.55 (m, 2H, CH_2), 3.25 (t, 2H, J=7.0 Hz, CH_2N), 6.97 (t, 2H, J=7.6 Hz, ArH), 7.15 (t, 1H, J=7.3 Hz, ArH), 7.4 (d, 1H, J=7.6 Hz, ArH), 9.27 (s, 1H, ArNH). IR (KBr) 3304, 3104, 2957, 2872, 1664. Anal. calcd for $C_{10}H_{12}N_2OSe$: C, 47.07; H, 4.74; N, 10.98. Found: C, 46.94; H, 4.53; N, 11.11%. Compound **1b**: yield 68%, mp 108–109°C, yellow prisms. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 0.85 (t, 3H, J=7.2 Hz, CH_3), 1.16–1.26 (m, 2H, CH_2), 1.41–1.46 (m, 2H, CH_2), 3.25 (t, 2H, J=7.0 Hz, CH_2N), 6.95 (d, 2H, J=7.3 Hz, ArH), 7.16 (t, 1H, J=7.7 Hz, ArH), 7.39 (d, 1H, J=7.7 Hz, ArH), 9.25 (s, 1H, ArNH). IR (KBr) 3309, 3084, 2987, 2965, 2872, 1645. Anal. calcd for $C_{11}H_{14}N_2OSe$: C, 49.08; H, 5.24; N, 10.41. Found: C, 48.91; H, 5.12; N, 10.83%. Compound **1c**: yield 54%, mp 96–98°C, white prisms. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 1.13–1.38 (m, 6H, CH_2), 1.50 (m, 2H, CH_2), 1.63–1.72 (m, 2H, CH_2), 3.72 (t, 1H, J=10.9 Hz, CHN), 6.88 (d, 2H, J=7.5 Hz, ArH), 7.09 (t, 1H, J=7.5 Hz, ArH), 7.31 (d, 1H, J=7.5 Hz, ArH), 9.23 (s, 1H, ArNH). IR (KBr) 3325, 3082, 2930, 2852, 1650. Anal. calcd for $C_{13}H_{16}N_2OSe$: C, 52.89; H, 5.46; N, 9.49. Found: C, 52.38; H, 5.21; N, 9.65%. Compound **1d**: yield 52%, mp 128–129°C, white prisms. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm) 6.99–7.05 (m, 2H, ArH), 7.27–7.38 (m, 3H, ArH), 7.57 (d, 1H, J=8.1 Hz, ArH), 7.82 (t, 3H, J=8.4 Hz, ArH), 10.43 (s, 1H, ArNH). IR (KBr): 3180, 3082, 2957, 1625, 1559, 1428, 1289, 1266, 744, 675. Anal. calcd for $C_{13}H_{10}N_2SSe$: C, 51.15; H, 3.30; N, 9.18. Found: C, 50.96; H, 3.63; N, 9.62%.

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11. A solution of bromine (8.9 g, 56 mmol) in dry 1,2-dichloromethane (100 ml) was added dropwise to a suspension of diselenide **7** (11.7 g, 50 mmol) at ice–salt bath temperature in the same solvent (250 ml) over 1 h. The reaction was stirred at room temperature for 24 h, the solvent and excess bromine were evaporated in vacuo. The residue was recrystallized from 1,2-dichloromethane to yield **8** (60%) as bright dark red plates, mp 146–147°C with decomp. (Ref. 12 139–141°C).

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13. A solution of compound **8** (0.788 g, 2.0 mmol) in dry 1,2-dichloromethane (20 ml) was added dropwise to a stirred solution of amine (6.3 mmol) at ice–salt bath temperature in the same solvent (80 ml) over a 30 min period. The reaction was continued at a temperature maintained below −5°C for 2 h, then the mixture was washed with water (3×20 ml). The layers were separated, the organic layer was dried over sodium sulfate and the solvent was evaporated in vacuo without heating. The residue was pure product **2**. Compound **2a**: yield 87%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 0.87 (t, 3H, J=7.5 Hz, CH_3), 1.49 (sextet, 2H, J=7.2 Hz, -CH_2-), 3.16 (t, 2H, J=7.2 Hz, CH_2N), 7.21 (dd, 2H, J=5.6 and 3.2 Hz, ArH), 7.45 (dd, 2H, J=5.6 and 3.2 Hz, ArH); IR (film) 3052, 2958, 2930, 2870, 1559, 1427, 741. Anal. calcd for $C_9H_{11}NSe_2$: C, 37.13; H, 3.81; N, 4.81. Found: C, 37.04; H, 3.74; N, 5.00%. Compound **2b**: yield 90%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 0.88 (t, 3H, J=7.2 Hz, CH_3), 1.30 (sextet, 2H, J=7 Hz, CH_2), 1.45 (q, 2H, J=7.2 Hz, CH_2), 3.18 (t, 2H, J=7.2 Hz, CH_2N), 7.21 (dd, 2H, J=5.5 and 3.2 Hz, ArH), 7.45 (dd, 2H, J=5.5 and 3.2 Hz, ArH) IR (film) 3052, 2956, 2929, 2869, 1559, 1427, 741. Anal. calcd for $C_{10}H_{13}NSe_2$: C, 39.36; H, 4.29; N, 4.59 Found: C, 39.04; H, 4.31; N, 4.80%. Compound **2c**: yield 96%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 0.88 (d, 6H, J=6.7 Hz, CH_3), 1.66–1.79 (m, 1H, CH), 3.00 (d, 2H, J=6.7 Hz, CH_2), 7.20 (dd, 2H, J=5.4 and 3.3 Hz, ArH), 7.45 (dd, 2H, J=5.4 and 3.3 Hz, ArH). IR (film) 3052, 2956, 2929,

2869, 1559, 1427, 741. Anal. calcd for $C_{10}H_{13}NSe_2$: C, 39.36; H, 4.29; N, 4.59. Found: C, 39.60; H, 4.60; N, 4.80%. Compound **2d**: yield 81%, yellow prisms, mp 59–61°C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 1.09 (s, 9H, CH_3), 7.14 (dd, 2H, $J=5.6$ and 3.2 Hz, ArH), 7.40 (dd, 2H, $J=5.6$ and 3.2 Hz, ArH). IR (KBr) 3048, 2967, 2923, 1555, 1423, 741. Anal. calcd for $C_{10}H_{13}NSe_2$: C, 39.36; H, 4.29; N, 4.59. Found: C, 39.32; H, 4.50; N, 4.85%. Compound **2e**: yield 86%, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) 0.86 (t, 3H, $J=7.5$ Hz, CH_3), 0.96 (d, 3H, $J=6.3$ Hz, CH_3), 1.16–1.36 (m, 1H, CH_2), 1.54–1.63 (m, 1H, CH_2), 2.78 (m, 1H, CH_3), 7.15 (dd, 2H, $J=5.7$ and 3.3 Hz, ArH), 7.39 (dd, 2H, $J=5.7$ and 3.3 Hz, ArH). IR (film) 3052, 2928, 2872, 1558, 1427, 741. Anal. calcd for $C_{10}H_{13}NSe_2$: C, 39.36; H, 4.29; N, 4.59. Found: C, 39.30; H, 4.10; N, 4.88%.