On the preparation of 1,2,5-selenadiazolo [3,4-*e*]indole and its [3,4-*f*] and [3,4-*g*] isomers through the Batcho–Leimgruber indole synthesis

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Abstract

1,2,5-Selenadiazolo[3,4-*e*]indole **6** was prepared by applying the Batcho−Leimgruber indole synthesis on 4-methyl-5-nitro-2,1,3-benzoselenadiazole **9**. This methodology was unsuccessful when applied to 5-methyl-6-nitro-2,1,3-benzoselenadiazole **14** for the synthesis of 1,2,5-selenadiazolo[3,4-*f*]indole **5**. An improvement on the preparation of 1,2,5-selenadiazolo[3,4-*g*]indole **3** is reported. An initial study on the bromination of **3** and the ^{77}Se-NMR chemical shifts of **3** and **6**, and of their precursors are presented.

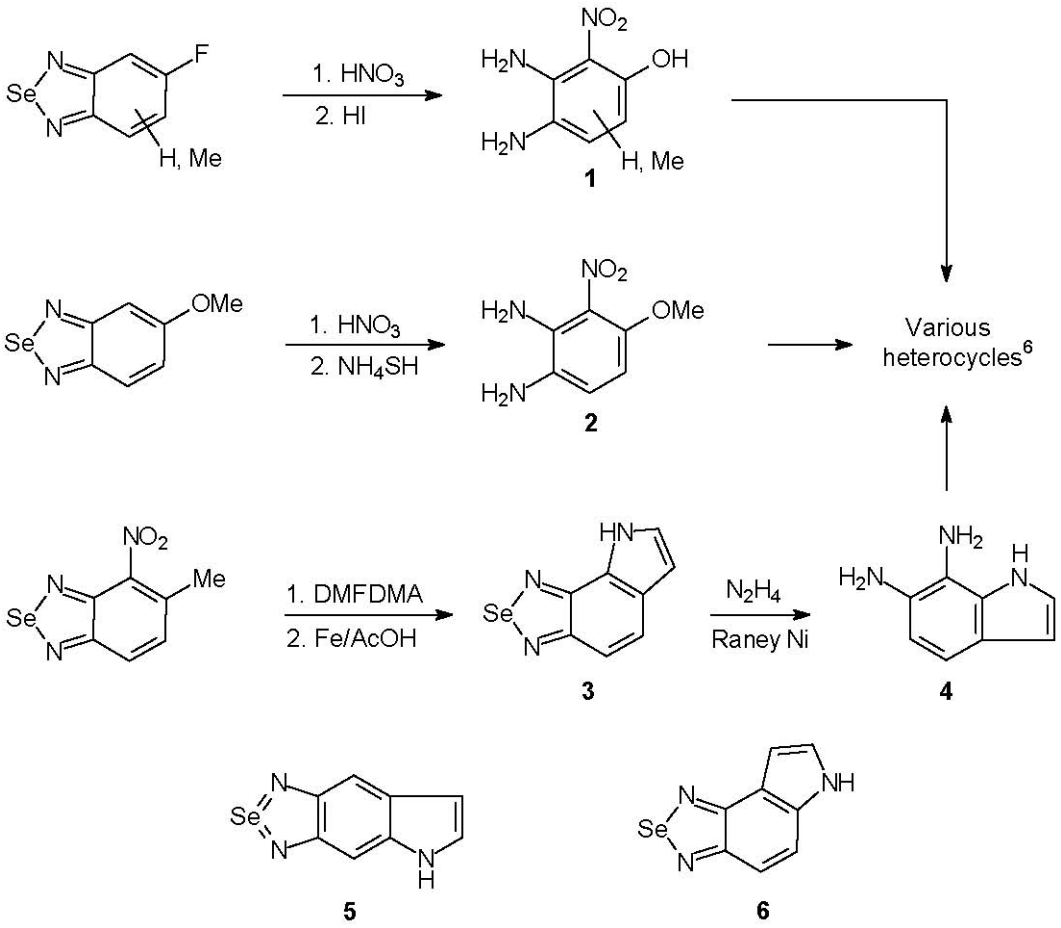
Keywords: Batcho-Leimgruber indole synthesis, 1,2,5-selenadiazolo[3,4-e]indole, ^{77}Se-NMR

Introduction

Derivatives of 1,2,5-selenadiazolobenzene (2,1,3-benzoselenadiazole, bsd) find plenty of pharmaceutical and other industrial applications, and they have also proved to be useful synthetic intermediates.[1,2] For example, the versatile diaminonitrophenols **1**[3] (Scheme 1), 4-methoxy-3-nitro-1,2-benzenediamine **2**[4] and indole-6,7-diamine **4**[5] are easily obtained by reductive deselenation of the corresponding bsd and then converted into other heterocycles.[3−6] In connection to our recent synthesis of selenadiazoloindole **3**[5] via the Batcho−Leimgruber (B–L) methodology,[7] we now report on our attempts to synthesize the unknown linear isomer 1,2,5-selenadiazolo[3,4-*f*]indole **5** and the angular isomer 1,2,5-selenadiazolo[3,4-*e*]indole **6** by applying the B–L method on the corresponding methylnitro-bsd.

Results and Discussion

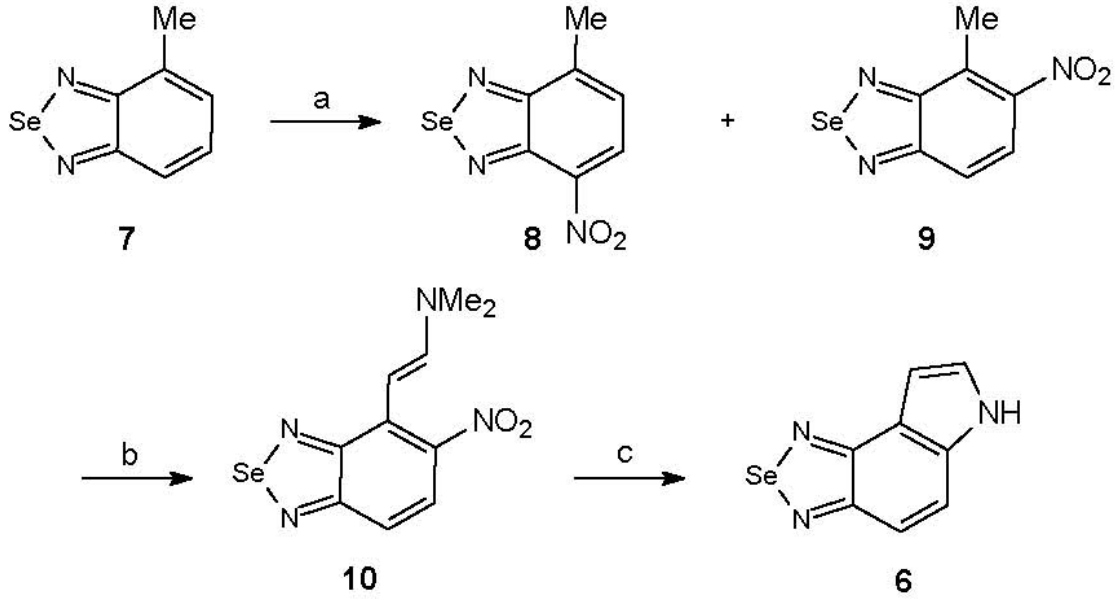
The title [3,4-*e*]-isomer **6** could be obtained from the readily available 4-methyl-bsd **7**[8] (Scheme 2). Nitration of **7** gave a mixture of 4-methyl-7-nitro-bsd **8**[9] and the 5-nitro isomer **9**.[9] The formation ratio of **8** and **9** could be influenced by varying the nitration conditions. For instance, treatment of a solution of **7** in 95% H_2SO_4 with an AcOH−fuming HNO_3 mixture afforded **8** and **9** in a 3:2 ratio at 75 ºC. This ratio was inverted to 2:3 when a solution of **7** in 80% H_2SO_4 was treated with 80% H_2SO_4−65% HNO_3 at ≤ 20 ºC. Separation of **8** and **9** was accomplished by fractional recrystallization from acetonitrile or toluene, and by steam distillation of the 2:3 mixture followed by one recrystallization to afford analytically pure **9**, which was then exposed to the B–L indole synthesis.



Scheme 1

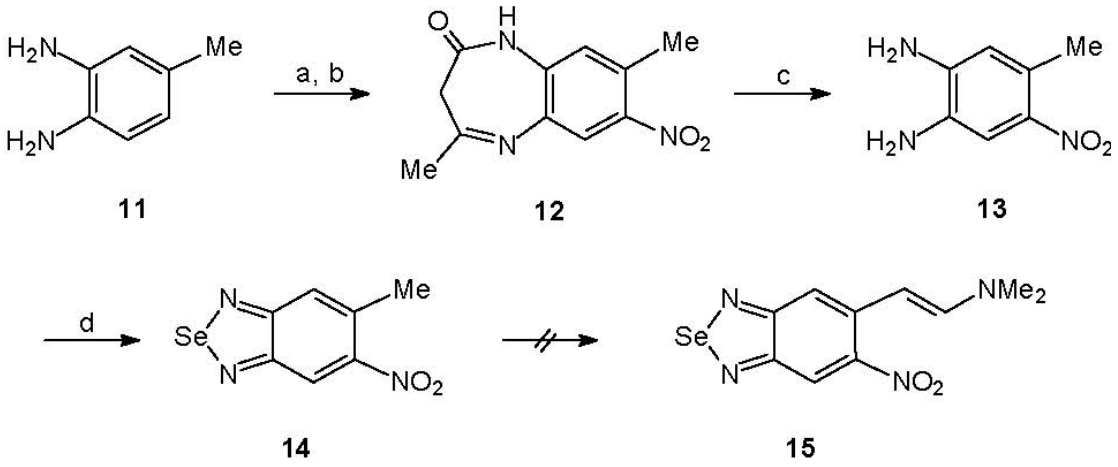
Treatment of **9** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) gave enamine **10** (blue coloured in chloroform), which was isolated and characterized as the *trans* isomer (J = 12.5 Hz). The ^{13}C-NMR signal from the *N*-methyl groups could only be detected at higher temperatures (≥ 80 ºC) presumably due to hindered rotation. The reductive ring closure of **10** into the title compound **6** was best accomplished by heating with Fe powder in toluene−glacial AcOH in the presence of silica gel, albeit in no more than 20% isolated yield. No better results were obtained under other reductive ring closure conditions such as hydrogenation over Pd-C or Raney nickel at various temperatures and pressures, or treatment with N_2H_4 hydrate and Raney nickel in various solvents. Further, attempts using $Na_2S_2O_4$ or $TiCl_3$ were not successful either.[5,10] Applying the B–L indole synthesis to a mixture of the nitro-bsd derivatives **8** and **9** did not alter the formation yield of the title [3,4-*e*] isomer **6**.

The conversion of **9** into **10** was less efficient than the recently reported[5] conversion of 4-nitro-5-methyl-bsd into (*E*)-5-[2-(dimethylamino)ethenyl]-4-nitro-bsd (red in chloroform) leading to the title [3,4-*g*] isomer **3**.[5] Addition of column chromatography silica gel[11] in the Fe powder-reduction of (*E*)-5-[2-(dimethylamino)ethenyl]-4-nitro-bsd[5] did not improve the yield (50−55%) but made the work-up of **3** much more convenient; this preferable procedure is therefore described in this paper.



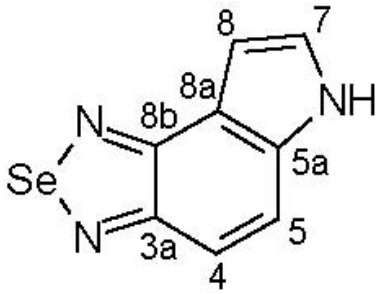
Scheme 2. (a) 80% H_2SO_4, 65% HNO_3, 0 → ≤ 20 ºC; (b) DMFDMA, MeCN, reflux, 5 h; (c) Fe, silica, PhMe/glacial AcOH (5:3 v/v), reflux 1 h

Preparation of the unknown linear [3,4-*f*] isomer **5** was attempted by applying the B−L reaction on 5-methyl-6-nitro-bsd **14** (Scheme 3). This derivative was prepared by treatment of 4-methyl-1,2-benzenediamine **11** with ethyl acetoacetate and subsequent nitration of the formed diazepinone to **12**, which on hydrolysis afforded **13**.[12] Treatment of the latter with SeO_2 afforded **14**, which has also been obtained from 5-methyl-2,4-dinitroaniline.[13]



Scheme 3. (a) $AcCH_2CO_2Et$, *o*-xylene, reflux, 16 h; (b) conc. H_2SO_4, $NaNO_3$, −10 ºC → rt; (c) MeOH/5.5 M HCl (1:1 v/v), reflux, 5 h; (d) aq. SeO_2, 1 M HCl, 85 ºC

In contrast to the conversion of **9** into **10**, treatment of **14**[12,13] with DMFDMA in refluxing CH_3CN gave no traces of enamine **15**. After prolonged reaction time, unchanged starting material could still be recovered together with unidentified material. Neither the use of DMF as solvent, nor addition of pyrrolidine[10] would facilitate the formation of **15**, presumably because of fixation of the C5−C6 bond and thus no stabilization of the enamine by the nitro group.
Proton- and carbon-NMR data for the two angular isomers **3** and **6** are collected in Table 1.



6

Table 1. ^{1}H- and ^{13}C-NMR shifts and HMBC correlations for **3** and **6**

Compound	^{13}C index	^{1}H index	δ_H (ppm)	δ_C (ppm)	HMBC cross peaks[a]
3	3a			159.5	$^{3}J_{C–H5}$, $^{2}J_{C–H4}$
	4	4	7.31	115.1	$^{2}J_{C–H5}$, $^{1}J_{C–H4}$
	5	5	7.73	126.8	$^{1}J_{C–H5}$
	5a			125.7	$^{3}J_{C–H7}$, $^{3}J_{C–H4}$
	6	6	6.57	104.5	$^{4}J_{C–H4}$, $^{3}J_{C–H5}$, $^{2}J_{C–H7}$, $^{1}J_{C–H6}$
	7	7	7.36	124.5	
		8	12.5		
	8a			124.6	$^{3}J_{C–H5}$, $^{3}J_{C–H7}$, $^{3}J_{C–H6}$
	8b			150.7	$^{4}J_{C–H5}$, $^{3}J_{C–H4}$
6	3a			155.7	$^{3}J_{C–H5}$, $^{2}J_{C–H4}$
	4	4	7.68	120.1	$^{2}J_{C–H5}$, $^{1}J_{C–H4}$
	5	5	7.38	116.1	$^{1}J_{C–H5}$
	5a			118.2	$^{3}J_{C–H4}$, $^{3}J_{C–H7}$, $^{3}J_{C–H8}$, $^{2}J_{C–H5}$
		6	11.8		
	7	7	7.35	123.6	$^{2}J_{C–H8}$
	8	8	6.93	104.2	$^{4}J_{C–H5}$, $^{2}J_{C–H7}$, $^{1}J_{C–H8}$
	8a			133.1	$^{3}J_{C–H5}$, $^{3}J_{C–H7}$, $^{2}J_{C–H8}$
	8b			158.7	$^{3}J_{C–H4}$

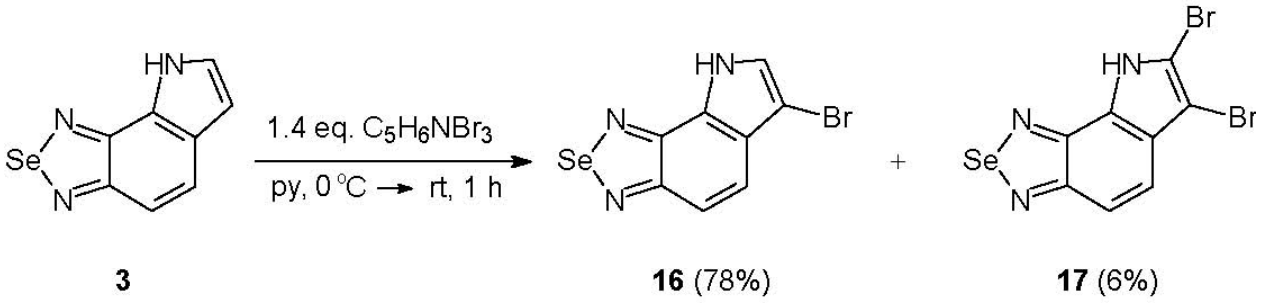
[a] $^{n}J_{C–HX}$ denotes the heteronuclear coupling (n = 1–4) between the indexed carbon and proton X.

The ^{77}Se-NMR chemical shifts of **3** and **6** and their precursors are shown in Table 2. ^{77}Se-NMR chemical shifts of other bsd derivatives were recently reported.[1]

Table 2. ^{77}Se- NMR chemical shifts

Compound	δ_{Se} (ppm)
5-Methyl-4-nitro-2,1,3-benzoselenadiazole[5]	1557.8
(*E*)-5-[2-(Dimethylamino)ethenyl]-4-nitro-bsd[5]	1526.3
1,2,5-Selenadiazolo[3,4-*g*]indole **3**[5]	1498.1
1,2,5-Selenadiazolo[3,4-*e*]indole **6**	1497.6
4-Methyl-5-nitro-2,1,3-benzoselenadiazole **9**	1571.5
(*E*)-4-[2-(Dimethylamino)ethenyl]-5-nitro-bsd **10**	1534.6
5-Methyl-6-nitro-2,1,3-benzoselenadiazole **14**	1585.1

Initial monobromination studies on the title compound **3** with various amounts pyridinium tribromide in pyridine were performed at 0 ºC → 20 ºC. When no more than 1.4 equivalents of brominating agent were used, the 6-bromo derivative **16**[14] (Scheme 4) and the 6,7-dibromo derivative **17**[14] were formed within 1 hour in a 14:1 ratio and in 84% yield. Treatment with 1.7 equivalents of $C_5H_6NBr_3$ afforded **16** in 50% and **17** in 25% yield within 2 hours, while use of 1.2 equivalents of brominating agent gave no dibromo derivative, 71% of **16** and 18% of unreacted **3** after 13 hours.



3 **16** (78%) **17** (6%)

Scheme 4

Experimental Section

General Procedures. Analytical TLC was performed using aluminium plates precoated with silica gel 60 F_{254} (Merck) and visualized by UV light and Van Urk's reagent.[15] Flash chromatography was carried out on silica gel 60 (35–70 μ, Grace). Melting points (uncorrected) were determined on a Büchi Melting Point B-545. All NMR spectra were recorded on a Bruker DPX 300 spectrometer at 25 ºC, unless otherwise stated. ^{1}H- and ^{13}C-NMR signals were

referenced to the solvent ($(CD_3)_2SO$ δ_H 2.50 and δ_C 39.5). Gradient HMBC and HMQC experiments were used for the assignments. Coupling constants are given in Hz and without sign. In ^{77}Se-NMR experiments, saturated aqueous selenous acid was used as an external reference (11.5 M, H_2SeO_3 δ_{Se} 1300.47)[16] and the samples were dissolved in and locked on $(CD_3)_2SO$. The IR-spectra were recorded (KBr) on a Perkin−Elmer FT-IR 1600 instrument. Electrospray-MS were recorded on a Perkin−Elmer API 150Ex spectrometer. Elemental composition was determined by EI-HRMS on a JEOL JMS-SX/SX102A instrument with direct insertion at 70 eV and an ion source temperature of 200 ºC.

Materials. Unless otherwise stated, these were commercial samples. All organic solvents were of analytical quality and used as purchased. Solvent mixtures are defined by volume ratios (v/v).

1,2,5-Selenadiazolo[3,4-*g*]indole (3). A vigorously magnetically stirred, dark red mixture of (*E*)-5-[2-(dimethylamino)ethenyl]-4-nitro 2,1,3-benzoselenadiazole[5] (2.20 g, 7.37 mmol), iron powder (6.99 g, 125 mmol) and silica gel (column chromatography grade, 35–70 mesh, 18.4 g) in toluene/glacial acetic acid 5:3 (100 mL) was cautiously heated under a nitrogen atmosphere. The reaction mixture turned brown and viscous before the temperature reached the boiling point; heating was discontinued. The mixture was allowed to cool to room T, diluted with ether and left stirred before being filtered first under vacuum and a second time by gravitation. The filtrate was washed successively with aqueous sodium disulfite, water, saturated sodium bicarbonate solution and brine. Drying ($MgSO_4$) and concentration gave indole **3** as a yellow solid (0.85 g, 52%). Its MS and ^{1}H-NMR data were in accordance to those previously reported.[5] For ^{13}C-NMR data see Table 1.

1,2,5-Selenadiazolo[3,4-*e*]indole (6). A vigorously magnetically stirred mixture of enamine **10** (97 mg, 0.33 mmol), iron powder (0.31 g, 5.53 mmol) and silica gel (column chromatography grade, 35–70 mesh, 0.81 g) in toluene/glacial acetic acid 5:3 (5 mL) was cautiously heated to reflux under nitrogen for 1 h. The reaction mixture was allowed to cool to room T, diluted with chloroform and filtered. The filter-cake was washed with chloroform and then ether. The filtrate was washed successively with aqueous sodium disulfite, saturated sodium bicarbonate solution until pH 8 and brine. Drying (Na_2SO_4), concentration onto silica and flash chromatography (hexane/EtOAc gradient 5:1–2:1) gave **6** as an orange solid (14 mg, 19%). Recrystallization from acetonitrile gave brown-yellow crystals of mp 171–2 °C; ^{1}H NMR δ 11.8 (1H, br s, *N*-H), 7.68 (1H, d, *J* = 9.3, 4-H), 7.36 (2H, m, 5-H and 7-H), 6.93 (1H, d, *J* = 2.84, 8-H); ^{13}C NMR: see Table 1; IR ν 3286, 3170, 3101, 1591, 1563, 1501, 1417, 1351, 1316, 896, 801, 745, 724 cm^{-1}; MS *m/z*: 224 (MH^+); EI-HRMS (M^+) calcd for $C_8H_5N_3Se$ 222.9649, found 222.9637.

4-Methyl-7-nitro-2,1,3-benzoselenadiazole (8). Recrystallization from toluene (see below) afforded **8** as golden-yellow needles: mp 235 °C (subl.) [lit.[9] 242 °C]; ^{1}H-NMR δ 8.42 (1H, d, *J*

= 7.5, 6-H), 7.52 (1H, dd, *J* = 7.5, 1.1, 5-H), 2.71 (3H, d, *J* = 0.8, Me); ^{13}C-NMR δ 160.4 (3a-C), 150.2 (7a-C), 140.9 (4-C), 139.2 (7-C), 127.9 (6-C or 5-C), 125.4 (5-C or 6-C), 18.8 (Me); IR ν 3055, 2978, 1611, 1510, 1332, 858, 824, 768, 733 cm^{-1}.

4-Methyl-5-nitro-2,1,3-benzoselenadiazole (9). A 3:2 mixture of the *ortho*- and *para*-nitro isomers was obtained by nitration[9] of 4-methyl-2,1,3-benzoselenadiazole.[8] The steam distillate of the crude mixture afforded **8** and **9** in a 1:16 ratio. Recrystallization of the evaporation residue from toluene furnished **9** as a pale yellow powder of mp 171–2 °C [lit.[9] 157.5–8.0 °C]; ^{1}H-NMR δ 8.00 (1H, d, *J* = 9.7, 6-H), 7.84 (1H, dd, *J* = 9.7, 0.6, 7-H), 2.85 (3H, s, Me); ^{13}C-NMR δ 159.01 (3a-C and 7a-C), 147.46 (5-C), 129.17 (4-C), 123.73 (6-C), 121.28 (7-C), 14.97 (Me); IR ν 3082, 1601, 1553, 1509, 1380, 1360, 1342, 1277, 827, 812, 741, 714 cm^{-1}.

(*E*)-4-[2-(Dimethylamino)ethenyl]-5-nitro-2,1,3-benzoselenadiazole (10). DMFDMA (92%, 2.10 mL, 14.5 mmol) was added dropwise from a syringe to a stirred slurry of **9** (1.67 g, 6.87 mmol) in acetonitrile (25 mL) at room T, under nitrogen and in oven-dried and septum-capped glassware. The mixture was heated to reflux for 3 h. More DMFDMA (92%, 2.00 mL, 13.8 mmol) was added. After 2 h at reflux, the reaction mixture was allowed to cool to room T and was allowed to stand. The precipitate was filtered off, washed with a small amount of ice-cold methanol and dried to give enamine **10** as dark brown crystals (0.76 g). Flash chromatography (hexane/EtOAc 2:1) of the evaporation residue from the mother liquor and collection of the blue band gave another 0.20 g of **10** (total yield 47%). Recrystallization of a sample from acetonitrile afforded sparkling, almost black needles of mp 165–6 °C; ^{1}H-NMR δ 9.06 (1H, d, *J* = 12.5, 2′-H), 7.98 (1H, d, *J* = 9.8, 6-H), 7.05 (1H, d, *J* = 9.8, 7-H), 6.77 (1H, d, *J* = 12.5, 1′-H), 3.11 (6H, s, *N*-Me); ^{13}C-NMR (T = 80 ºC) δ 160.3 (7a-C), 157.7 (3a-C), 155.9 (2′-C), 136.4 (5-C), 132.6 (4-C), 126.4 (6-C), 112.4 (7-C), 91.9 (1′-C), 40.46 (*N*-Me$_2$); IR ν 3082, 2913, 1595, 1532, 1474, 1408, 1388, 1296, 1228, 1208, 1094, 827, 806 cm^{-1}.

5-Methyl-6-nitro-2,1,3-benzoselenadiazole (14). To a stirred, red solution of diamine **13**[12] (3.58 g, 21.4 mmol) in 1 M HCl (75 mL) at 85 °C was added aqueous selenium dioxide (1.33 M, 32.2 mL, 42.8 mmol) in portions. After the last addition, TLC (hexane/EtOAc 2:1) showed complete consumption of the starting material. The reaction mixture was cooled, filtered, washed with plenty of water and dried to give **14** as a light brown solid (4.1 g, 79%). A small sample was recrystallized from ethyl acetate: mp 165–6 °C [lit.[13] 165–6 °C]; ^{1}H-NMR δ 8.51 (1H, s, 7-H), 7.91 (1H, d, *J* = 0.5, 4-H), 2.52 (3H, d, *J* = 0.7, Me); ^{13}C-NMR δ 159.5 (3a-C), 156.6 (7a-C), 151.2 (6-C), 130.8 (5-C), 124.5 (4-C), 118.9 (7-C), 18.9 (Me); IR ν 3102, 1610, 1528, 1491, 1385, 1339, 1281, 823, 764 cm^{-1}.

Acknowledgements

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References

1. Grivas, S. *Curr. Org. Chem.* **2000**, *4*, 707.
2. (a) Elvidge, J. A.; Newbold, G. T.; Percival, A.; Senciall, I. R. *J. Chem. Soc.* **1965**, 5119. (b) Ralph, J. T. *Synth. Commun.* **1989**, *19*, 1381.
3. Tian, W.; Grivas, S.; Olsson, K. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 257.
4. Grivas, S.; Tian, W. *Acta Chem. Scand.* **1992**, *46*, 1109.
5. Edin, M.; Grivas, S. *ARKIVOC* **2000**, *i*, 1.
6. (a) Grivas, S.; Tian, W.; Ronne, E.; Lindström, S.; Olsson, K. *Acta Chem. Scand.* **1993**, *47*, 521. (b) Grivas, S.; Tian, W.; Andersson, R. *J. Chem. Res.* **1992**, (S) 328; (M) 2701. (c) Tian, W.; Grivas, S. *Synthesis* **1992**, 1283. (d) Tian, W.; Grivas, S. *J. Heterocycl. Chem.* **1992**, *29*, 1305.
7. Batcho, A. D.; Leimgruber, W. *Org. Synth. Coll. Vol.* **1990**, *7*, 34. (b) Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195.
8. Kochansky, J. P.; Cohen, C. F.; Lusby, W. R.; Svoboda, J. A.; Feldmesser, J.; Wright, F. C. *J. Agric. Entomol.* **1988**, *5*, 131.
9. Pesin, V. G.; Muravnik, R. S. *Latv. PSR Zinat. Akad. Vestis Khim. Ser.* **1964**, 726; *Chem. Abstr.* **1965**, *63*, 4279h.
10. Sundberg, R. J. In *Best Synthetic Methods*, *Indoles*; Academic Press: 1996; pp 7−11.
11. Sinhababou, A. K.; Borchardt, R. T. *J. Org. Chem.* **1983**, *48*, 3347; Kawase, M.; Sinhababu, A. K.; Borchardt, R. T. *J. Heterocycl. Chem.* **1987**, *24*, 1499.
12. Solomko, Z. F.; Chmilenko, T. S.; Sharbatyan, P. A.; Shtemenko, N. I.; Khimyuk, S. I. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1978**, *14*, 100.
13. Efros, L. S.; El'zow, A. V. *Zh. Obshch. Khim.* **1958**, *28*, 2172.
14. **16.** ^{1}H-NMR (DMSO-d_6) δ 12.9 (1H, br s, *N*-H), 7.58 (2H, m, 7-H and 4-H or 5-H), 7.43 (1H, d, J = 9.3, 5-H or 4-H); ^{13}C-NMR (DMSO-d_6) δ 159.4, 150.0, 125.7, 124.1, 123.6, 123.2, 116.3, 91.9. **17**: ^{1}H-NMR (DMSO-d_6) δ 13.8 (1H, br s, *N*-H), 7.55 (1H, d, J = 9.3, 4-

H or 5-H), 7.45 (1H, d, *J* = 9.3, 5-H or 4-H).

15. Stahl, E.; Kaldewey, H. *Hoppe-Seylers Z. Physiol. Chem.* **1961**, *323*, 182.
16. Milne, J. *Magn. Reson. Chem.* **1993**, *31*, 652.