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First synthesis of 1,3-oxaselenepanes

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ABSTRACT

The first synthesis of 1,3-oxaselenepane derivatives by the reaction of aryl isoselenocyanates with 4-bromobutanol in the presence of sodium hydride in THF as a one-pot reaction is described. The *Z*/*E* isomerism for the exocyclic carbon–nitrogen double bond in the selenium heterocycles was observed for the first time.

In recent years, interest in synthesis of selenium-containing compounds has increased because of their interesting reactivities[1] and their potential biological activity. The biological and medicinal properties of selenium and organoselenium compounds are increasingly appreciated, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.[2] The selenoureas[3] and selenoamides[3a,4] have been extensively studied for the synthesis of selenium-containing heterocycles. In this context, isoselenocyanates[5] have been emerged as a powerful tool for the synthesis of selenium-containing heterocycles, since they are easy to prepare and store and are safe to handle. Our group has shown the utility of isoselenocyanates in the synthesis of a variety of four-,[6] five-,[7] or six-membered[8] selenium-containing heterocycles.

In contrast, only a few examples for the synthesis of seven-membered selenium-containing heterocycles, such as 1,3-selenazepines, have been reported in the literature.[9] For example, our group has reported the synthesis of β-lactam-fused 1,3-selenazepines,[9a,b] whereas the Russian team has published an article concerning the synthesis of 1,3-selenazepane fused with a pyrimidinone system.[9c] Heimgartner et al. reported the synthesis of 1,3-selenazepanes by the reaction of isoselenocyanates with 5-chlorobutylamine.[9d] However, it is surprising to note that there is no report on the synthesis of seven-membered selenium-containing heterocycles such as 1,3-oxaselenepanes. Herein we report for the first time, the synthesis of 1,3-oxaselenepanes by the reaction of isoselenocyanates with 4-bromobutanol and its *Z* and *E* isomerism.

For our approach substituted alkyl and aryl isoselenocyanates **1** were prepared by reactions of N-substituted formamides with an excess of triphosgene, selenium, and triethylamine according to the previous literature.[10] First, the reaction of phenyl isoselenocyanate **1a** with 4-bromobutanol using 2.5 equiv of NaH was examined in CH_2Cl_2 at 0 °C to rt and the cyclized product **2a** was obtained only in traces after work-up of the reaction mixture. To improve the yield of the reaction, different conditions were then screened. Finally, 1.5 equiv of 4-bromobutanol and 1.8 equiv of NaH were suitable for the cyclization reaction, furthermore the reaction was influenced by the solvent used and the best result was obtained when the reaction was carried out in THF (29%, entry 1, Table 1) (Scheme 1).[11] The use of 4-chlorobutanol in the present reaction leads to the formation of required 1,3-oxaselenepanes **2a** in traces.[12]

The compound **2a** was isolated as an inseparable mixture of *Z* and *E* isomers (6.9:1 ratio) at the imine position. The structure of **2a** was elucidated by studies of IR, ^1H, ^{13}C, ^{77}Se NMR, COSY, HMQC, HMBC and NOESY, MS, elemental analysis, and X-ray analysis. All attempts to separate the *Z* and *E* isomers were failed. In the ^{77}Se NMR spectra of the 1,3-oxaselenepane **2a**, two ^{77}Se signals were observed δ 361.4 for the *Z* isomer and δ 383.3 for *E* isomer which were at a higher field as compared with ^{77}Se signals of selenocarbonyl compounds (δ 1420–2131).[13] The values are typical for a C–Se single bond with an sp^3 selenium atom and not for a C=Se double bond with an sp^2 selenium atom.[14] Under similar reaction conditions, the reactions of six isoselenocyanates **1** with 4-bromobutanol gave the 2-imino-1,3-oxaselenopanes **2** as mixture of *Z* and *E* isomers in 4–32% yields (Table 1). Aryl isoselenocyanates **1a–d** provided the corresponding 1,3-oxaselenepanes **2a–d** in moderated yields (entries 1–4). The benzyl isoselenocyanate **1e** afforded the 1,3-oxaselenepanes **2e** in 23% yield (entry 5). The use of cyclohexyl isoselenocyanate **1f** in the reaction was found to be difficult and the cyclized product 1,3-oxaselenepanes **2e**

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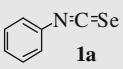
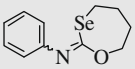
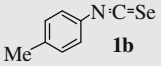
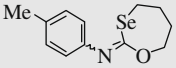
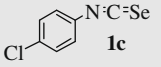
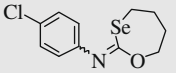
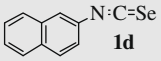
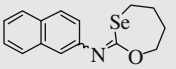
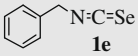
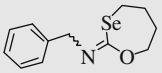
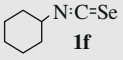
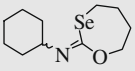
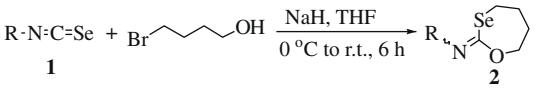
Table 1
Synthesis of 1,3-oxaselenepanes **2**

Entry	Isoselenocyanate	Product	Yield[a] (%)	Ratio (*Z*/*E*)[b]
1	 **1a**	 **2a**	29	6.9/1
2	 **1b**	 **2b**	20	6.9/1
3	 **1c**	 **2c**	32	4.9/1
4	 **1d**	 **2d**	28	7.9/1
5	 **1e**	 **2e**	23	2.1/1
6	 **1f**	 **2f**	4	6.9/1

[a] Isolated yield.
[b] *Z*/*E* ratio was determined by ^{1}H NMR.



Scheme 1.

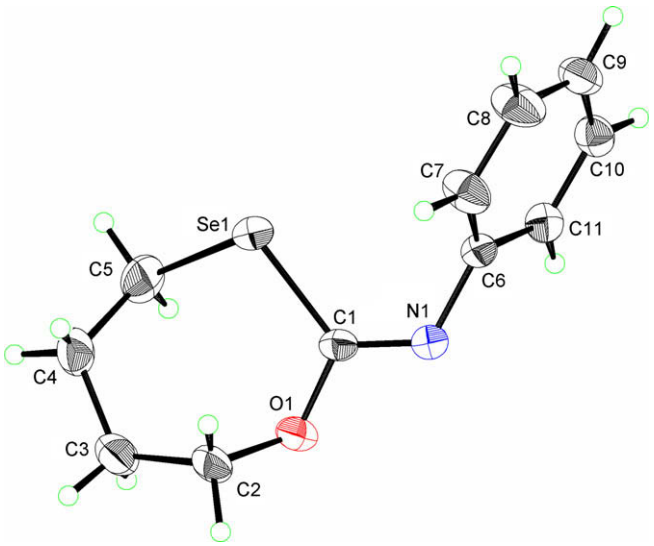


Figure 1. Crystal structure of (*Z*)-*N*-(1,3-oxaselenepan-2-ylidene)aniline (**2a**).

was obtained only in 4% yield (entry 6). The structures of products **2b–f** were determined by comparing the spectral data with those of **2a**. In all cases the *Z* isomer was the major product. Generally the selenium containing heterocyclic compounds having an exocyclic C=N bond were isolated as the *Z* isomers only.[15] To the best of our knowledge this is the first time we found the formation of the *E* isomer along with the *Z* isomer.

To gain a more detailed insight into the structure, the 1,3-oxaselenepane **2a** was crystallized from EtOAc–hexane and single crystals suitable for X-ray analysis were grown by slow evaporation of the solvent.[16] An ORTEP drawing, depicted in Figure 1, shows the molecular structure of the **2a**.[17] Compound **2a** possesses an exocyclic carbon–nitrogen double bond with *Z*-configuration. The bond angle of the selenium atom C1–Se1–C5 was 101.6(2)°. The length of Se1–C1 bond (1.947(6) Å) is consistent with the typical Se–C bond (1.94 Å), whereas the bond length of Se1–C5 bond (1.919(5) Å) is shorter than the typical Se–C bond (1.94 Å).[18] The bond length of C1–N1 in **2a** is 1.248(6) Å, which clearly shows that this is a double bond.

In conclusion, we report the first synthesis of 1,3-oxaselenepane derivatives and their *Z*/*E* isomerism for the exocyclic C=N bond.

Acknowledgments

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11. Typical synthesis procedure and spectral data of selected compounds. *N-(1,3-oxaselenepan-2-ylidene)aniline* (**2a**): To a stirred solution of NaH (60% in oil, 36.0 mg, 0.90 mmol) in dry THF (2.0 mL) was added phenyl isoselenocyanate (91 mg, 0.50 mmol) at 0 °C. After 10 min 4-bromobutanol (>80% in THF, 100 μL, 0.75 mmol) was added and stirring was continued for 6 h at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with ethyl acetate, and washed with water and brine. The combined organic layer was dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel with ethyl acetate/*n*-hexane (1/10→1/5) as the eluent to give **2a** (35 mg, yield 29%, *Z*/*E* = 6.9/1). Mp 64–65 °C; IR (KBr): 1621 cm^{-1}; For *Z*-isomer **2a**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.94–2.00 (2H, m, CH_2), 2.23–2.30 (2H, m, CH_2), 2.87 (2H, t, J = 5.5 Hz, $^2J(^{77}Se–^1H)$ = 29.2 Hz, CH_2), 4.43 (2H, t, J = 4.8 Hz, CH_2), 6.85 (2H, d, J = 7.4 Hz, Ar), 7.11 (1H, t, J = 7.4 Hz, Ar), 7.31 (2H, t, J = 7.4 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.2($^1J(^{77}Se–^{13}C)$ = 60.0 Hz), 29.8, 30.5, 71.5, 120.9, 124.2, 128.9, 148.3, 159.9; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 361.4; For *E*-isomer **2a**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.86–1.91 (2H, m, CH_2), 2.28–2.33 (2H, m, CH_2), 2.97 (2H, t, J = 5.5 Hz, $^2J(^{77}Se–^1H)$ = 28.5 Hz, CH_2), 4.35 (2H, t, J = 4.8 Hz, CH_2), 7.03 (2H, d, J = 8.0 Hz, Ar), 7.05 (1H, t, J = 7.5 Hz, Ar), 7.26 (2H, t, J = 7.4 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.7, 29.3, 30.5, 71.4, 122.4, 123.7, 128.4, 146.7, 157.8; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 383.3; MS (EI): m/z = 255 [M^+]; HRMS(EI): calcd for $C_{11}H_{13}NOSe$: 255.0167, found: 255.0146.
4-Chloro-N-(1,3-oxaselenepan-2-ylidene)aniline (**2c**): Yield: 32%; Mp. 96–97 °C; IR (KBr): 1626 cm^{-1}; For *Z*-isomer **2c**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.94–2.00 (2H, m, CH_2), 2.24–2.30 (2H, m, CH_2), 2.90 (2H, t, J = 5.5 Hz, $^2J(^{77}Se–^1H)$ = 29.2 Hz, CH_2), 4.43 (2H, t, J = 4.6 Hz, CH_2), 6.78 (2H, d, J = 8.6 Hz, Ar), 7.26 (2H, d, J = 8.6 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.4 ($^1J(^{77}Se–^{13}C)$ = 69.9 Hz), 29.8, 30.4, 71.7, 122.3, 129.0, 129.1, 146.3, 160.6; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 362.1; For *E*-isomer **2c**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.88–1.93 (2H, m, CH_2), 2.27–2.34 (2H, m, CH_2), 2.98 (2H, t, J = 5.5 Hz, $^2J(^{77}Se–^1H)$ = 28.7 Hz , CH_2), 4.37 (2H, t, J = 4.6 Hz, CH_2), 6.98 (2H, d, J = 8.6 Hz, Ar), 7.22 (2H, d, J = 8.6 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.8, 29.3, 30.4, 71.6, 124.0, 128.5, 129.2, 145.2, 158.6; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 385.9; MS (EI): m/z = 289 [M^+]; Anal. Calcd for $C_{11}H_{12}ClNOSe$: C, 45.77; H, 4.19; N, 4.85. Found: C, 45.47; H, 4.68; N, 5.01.
N-(1,3-Oxaselenepan-2-ylidene)-1-phenylmethanamine (**2e**): Yield: 23%; IR (KBr): 1640, 1686 cm^{-1}; For *Z*-isomer **2e**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.86–1.94 (2H, m, CH_2), 2.23–2.31 (2H, m, CH_2), 2.96 (2H, t, J = 5.1 Hz, $^2J(^{77}Se–^1H)$ = 28.9 Hz, CH_2), 4.30 (2H, t, J = 5.1 Hz, CH_2), 4.41 (2H, s, CH_2), 7.18–7.35 (5H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.9, 30.1, 30.5, 56.8, 71.0, 126.5, 127.6, 128.3, 139.3, 158.8; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 335.1; For *E*-isomer **2e**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.86–1.91 (2H, m, CH_2), 2.28–2.32 (2H, m, CH_2), 2.89 (2H, t, J = 5.0 Hz, CH_2), 4.36 (2H, t, J = 5.0 Hz, CH_2), 4.54 (2H, s, CH_2), 7.18–7.25 (5H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.3, 29.6, 30.8, 52.4, 70.5, 126.4, 127.8, 128.2, 140.3, 156.6; ^{77}Se NMR (95 MHz, $CDCl_3$): δ 370.2; MS (FAB): m/z = 270 [M^++1]$^+$; Anal. Calcd for $C_{12}H_{15}NOSe$: C, 53.74; H, 5.64; N, 5.22. Found: C, 53.93; H, 5.71; N, 5.70.
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16. X-ray crystallographic data for **2a**. Single-crystal X-ray diffraction: Rigaku AFC7R Mercury CCD area-detector diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). The structures were solved by direct methods (SIR97, Altomare, A.; Burla, M.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115) and refined by full-matrix least-squares on F^2 (Sheldrick, G. M. SHELEX-97, Program for Crystal Structure refinement, Universitat Göttingen, 1997). All non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined by a riding model. Empirical absorption corrections were applied. Single crystal was grown from EtOAc–hexane: $C_{11}H_{13}NOSe$, M_r = 331.13, Colorless crystal (0.20 × 0.20 × 0.15 mm^3), Crystal system: Monoclinic, space group: '*C*2/*c*', a = 19.749(16), b = 8.326(6), c = 13.644(11) Å, β = 99.769(12)°, V = 2211(3) $Å^3$, Z = 8, μ = 3.36 mm^{-1}, F_{000} = 1024, D_{calcd} = 1.527 Mg/m^3, Reflections collected: 8747, independent reflections: 2511 unique (R_{int} = 0.0449), 127 parameters, θ range for data collection 3.2–27.48°. Limiting indices −23*h*25, −10*k*10, −17*l*12, largest max./mim. in the final difference Fourier synthesis 1.29 e $Å^{-3}$/−0.65 e $Å^{-3}$, max./min. transmission 0.6323/0.5527, T = 296(2) K, R_1 = 0.0777 [$I > 2\sigma(I)$], wR_2 = 0.1255. Goodness-of-fit on F^2 1.192. R indices (all data) R_1 = 0.1062, wR_2 = 0.1353.
17. CCDC 715134 for **2a** contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
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