1,3-Selenazole

Harald Below,*[a] Wolf-Diethard Pfeiffer,[b] Karlheinz Geisler,[b] Michael Lalk,[c] and Peter Langer*[b,d,e]

Dedicated to Professor Ehrenfried Bulka on the occasion of his 80th birthday

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The parent 1,3-selenazole was prepared by cyclization of selenoformamide with α-bromoacetaldehyde.

1,3-Selenazoles are of pharmacological relevance, due to their antibiotic and cancerostatic activity.[1] A prominent example is the antibiotic selenazofurin – a C-glycosyl selenazole.[1a] Substituted 1,3-selenazoles are known for a long time;[2] they have been prepared mainly by cyclization of α-halo ketones with selenocarboxylic amides.[3] In contrast, 2-unsubstituted 1,3-selenazoles are rare, owing to their instability. Notably, parent 1,3-selenazole is unknown to date and its synthesis represents a long-standing problem. Herein, we wish to report a new method for the preparation of 2-unsubstituted 1,3-selenazoles and its application to what is, to the best of our knowledge, the first synthesis of parent 1,3-selenazole.

Two strategies for the synthesis of parent 1,3-selenazole are viable: Firstly, the removal of a functional group at C-2 and, secondly, the direct cyclization of selenoformamide (**1**) with an appropriate 1,2-dielectrophile. The first strategy has been successfully applied to the synthesis of 2-unsubstituted 1,3-selenazoles. For example, 4-methyl-1,3-selenazole has been prepared by oxidation of 2,4-dimethyl-1,3-selenazole to give selenazole-2-carboxylic acid and subsequent decarboxylation of the latter.[4] Recently, we have reported the synthesis of 2-unsubstituted 1,3-selenazoles by base-mediated fragmentation of 2-acyl-4-aryl-1,3-selenazoles.[5] Attempts to prepare the unsubstituted parent 1,3-selenazole from selenazol-2-amine by reduction of a diazonium compound failed.[6] The second strategy, the employment of selenoformamide, is very attractive because of its simplicity. In a pioneering work, Haginawa reported the formation of 4-methyl-1,3-selenazole, albeit in only 3% yield, by reaction of HCN, H_2Se and chloroacetone.[7,8] In 1984, two of us reported the first synthesis of selenoformamide.[9] To the best of our knowledge, only two synthetic applications of selenoformamide have been reported to date, owing to its unstable nature and difficult handling.[10] Weber and Hartmann reported the transformation of selenoformamide into an 1,3-oxaseleno derivative.[11] We have recently reported the cyclization of *p*-nitrophenacyl bromide with selenofomamide to give 4-(*p*-nitrophenyl)-1,3-selenazole; the latter could be isolated by precipitation, due to its low solubility.[12] Therefore, our first aim was the application of this methodology to the synthesis of related 2-unsubstituted 1,3-selenazoles.

Selenoformamide (**1**) was prepared, as previously reported,[13] by reaction of neat formamide with (freshly prepared) phosphorus(v) selenide (P_2Se_5); during our present study we have found that the reaction is considerably accelerated by use of ultrasound. Eventually, the cyclization of α-halo ketones **2a**–**e** with **1** afforded, under optimized conditions, the desired 2-unsubstsituted 1,3-selenazoles **3a**–**e** (Scheme 1, Table 1). The isolation of the products proved difficult, due to their good solubility and unstable nature; in addition, the reaction conditions had to be optimized individually for the synthesis of each derivative (see Supporting information; for Supporting informations see also the footnote on the first page of this article). To a methanol

[a] Institute of Hygiene and Environmental Medicine, Ernst-Moritz-Arndt-University Greifswald,
Walter-Rathenau-Str. 49A, 17487 Greifswald, Germany
Fax: +49-3834-515541
E-mail: below@uni-greifswald.de
[b] Institute of Chemistry and Biochemistry, Ernst-Moritz-Arndt-University Greifswald,
Soldmannstr. 16, 17487 Greifswald, Germany
[c] Institute of Pharmacy, Ernst-Moritz-Arndt-University Greifswald,
Jahnstr.17, 17487 Greifswald, Germany
[d] Institute of Chemistry, University of Rostock,
Albert-Einstein-Str. 3a, 18059 Rostock, Germany
Fax: +49-381-4986412
E-mail: peter.langer@uni-rostock.de
[e] Leibniz-Institut für Organische Katalyse an der Universität Rostock e. V. (IfOK),
Albert-Einstein-Str. 29a, 18059 Rostock, Germany
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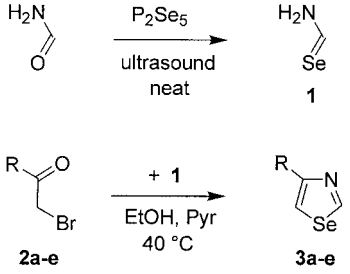
solution of the ketone was portionwise added crude selenoformamide until the reaction was complete (monitoring of the reaction by HPLC). The cyclizations were carried out in the presence of either pyridine or the acidic ion exchange resin Amberlite IR-120; the absence of base or the use of sodium acetate resulted in formation of considerable amounts of diphenacyl selenides $(ArCOCH_2)_2Se$. The latter were formed as side-products, even under optimized conditions, and had to be separated by precipitation. The 1,3-selenazoles were finally isolated by crystallization or by preparative HPLC.



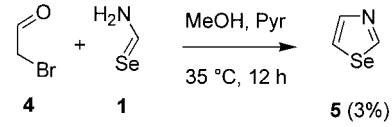
Scheme 1. Cyclization of selenoformamide with α-bromo ketones.

Table 1. Products and yields.

3	R	Yield [%] 3[a]	Method[b]
a	4-ClC_6H_4	13	A
a	4-ClC_6H_4	22	B
b	4-BrC_6H_4	9	A
c	4-FC_6H_4	20	B
d	4-(MeO)C_6H_4	6	B
e	4-$(O_2N)C_6H_4$	28	A

[a] Isolated yields. [b] A: Amberlite IR-120, B: pyridine.

The synthesis of parent 1,3-selenazole by our methodology proved to be difficult, due to its unstable nature and volatility. Eventually, 1,3-selenazole (**5**) was successfully prepared by pyridine-mediated cyclization of selenoformamide with bromoacetaldehyde (**4**) which was generated by treatment of 1-bromo-2,2-diethoxyethane with HCl (Scheme 2). 1,3-Selenazole was obtained in 3% yield as a brownish, unstable oil; all attempts to remove a rest of solvent resulted in decomposition. A small amount of an unknown impurity could not be removed, due to decomposition. The boiling point was estimated by gas chromatography (128.5 °C) and the structure was confirmed by spectroscopic methods. In the ^1H NMR spectrum ($CDCl_3$), three signals are observed at δ = 8.01 (5-H), 8.06 (4-H) and 9.92 (2-H) ppm exhibiting the expected coupling constants J_{HH} and J_{SeH}. A low-field shift is observed for 2-H and 5-H relative to the respective signals of thiazole [$CDCl_3$; δ = 7.41 (5-H), 7.98 (4-H) and 8.88 (2-H)]. The ^{13}C NMR spectrum of 1,3-selenazole shows three signals at δ = 124.61 (C-5), 143.90 (C-4) and 159.28 (C-2) ppm. As expected, a single signal is observed by ^{77}Se NMR (δ = 728.9 ppm). The mass spectrum (EI) exhibits the characteristic pattern for the presence of a selenium atom; the exact mass for C_3H_4NSe was confirmed by HR-FTICR.



Scheme 2. Synthesis of parent 1,3-selenazole.

Experimental Section

Synthesis of 1,3-Selenazole (5): 1-Bromo-2,2-diethoxyethane (2.92 g, 14.8 mmol) was hydrolyzed by stirring with concentrated hydrochloric acid (2.9 mL) at 50–60 °C for 30 min. The mixture was cooled to 10 °C and MeOH (10 mL) was added. To the solution was portionwise added pyridine (0.82 mL); subsequently, an MeOH solution (10 mL) of selenoformamide (**1**) was portionwise added at 35 °C. The progress of the reaction was monitored by HPLC. After stirring at 35 °C for 12 h, the mixture was poured into H_2O and an aqueous solution of NaOH (10 M) was added until the solution was adjusted to pH = 3.6. The solution was extracted with diethyl ether (4 × 50 mL) and the combined organic layers were extracted with hydrochloric acid (3.5%, 50 mL). To the aqueous layer was added an aqueous solution of NaOH (10 M) until the solution was adjusted to pH = 3.6; subsequently, the solution was extracted again with diethyl ether. This procedure was repeated until pyridine could not be detected anymore by HPLC. The combined organic layers were dried (Na_2SO_4), filtered and most of the solvent was removed by distillation in vacuo to give a brownish oil (0.050 g, 3%), b.p. 128.5 °C (determined by gas chromatography). All attempts to remove a rest of solvent resulted in decomposition (product/solvent = 2:1). A small amount of an unknown impurity could not be removed. IR (KBr): $\tilde{\nu}$ = 728 (m), 789 (s), 844 (w), 1020 (m), 1396 (s), 1438 (m), 1489 (s), 1651(m), 2926 (w), 3074 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, $J_{4,5}$ = 3.7, $^2J_{SeH}$ = 50.23, 1 H, 5-H), 8.06 (q, $^3J_{SeH}$ = 65.9 Hz, 1 H, 4-H), 9.92 (d, $J_{2,5}$ = 0.8, $^2J_{SeH}$ = 60.29, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.61 (C-5), 143.90 (C-4), 159.28 (C-2) ppm. ^{77}Se NMR ($CDCl_3$, 60% Me_2Se in $CDCl_3$): δ = 728.9 ppm. MS (EI, 70 eV): *m/z* (%) = 128/129 (18/15), 130/132 (48/100), 134 (15) [M^+], 108 (9), 106 (50), 104 (24), 103 (8), 102 (9), 82 (3), 80 (18), 78 (7), 77 (3), 76 (3), 51 (2). HR-FTICR-MS: calcd. for C_3H_4NSe [M + H]$^+$: 133.95089; found: 133.95017 (Δm = 5.4 ppm).

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