Efficient Synthesis of 2-Unsubstituted 1,3-Selenazoles

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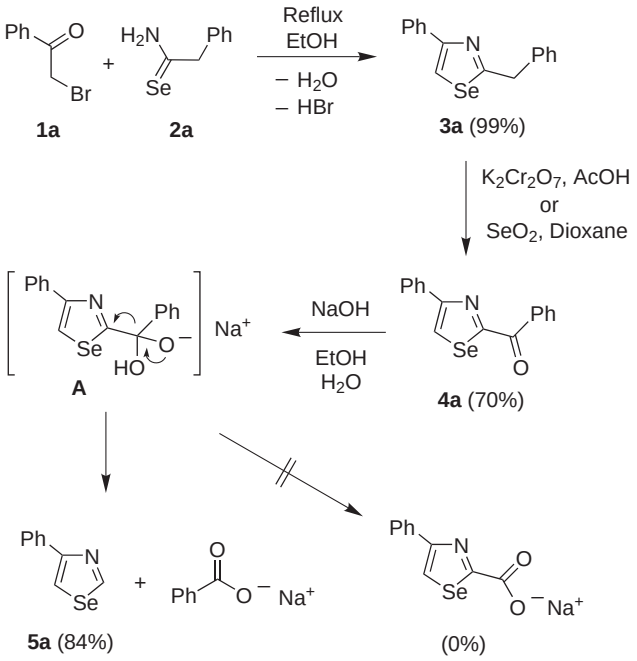
Abstract: Two new and efficient methods for the synthesis of 2-unsubstituted 1,3-selenazoles, the fragmentation of 2-benzoyl-1,3-selenazoles and the cyclization of α-bromoketones with selenoformamide, are reported.

Key words: cyclization, fragmentation, selenium heterocycles, oxidation, 1,3-selenazoles

1,3-Selenazoles are of considerable pharmacological relevance.[1–3] The synthesis of 2-unsubstituted 1,3-selenazoles has been a long-standing problem and only relatively few derivatives have been prepared to date. Haginiwa et al. have obtained 4-methylselenazole by reaction of HCN, H_2Se and chloroacetone, however, in only 3% yield.[4] Recently, Sonoda et al. have reported the synthesis of 2-unsubstituted 1,3-selenazoles by reaction of ethyl *iso*-cyanoacetate with *iso*selenocyanates.[5] However, this method is limited to the synthesis of 4,5-disubstituted derivatives. In addition, only arylamino-substituted selenazoles could be prepared, due to the nature of the starting materials employed. Herein, we wish to report a new and convenient method for the synthesis of 2-unsubstituted 1,3-selenazoles which relies on the fragmentation of novel 2-benzoyl-1,3-selenazoles.[6] In addition, a second approach to 2-unsubstituted 1,3-selenazoles by cyclization of selenoformamide with α-bromoketones is reported.

The cyclization of α-bromoacetophenone (**1a**) with selenophenylacetic amide (**2a**), prepared from phenylacetonitrile and P_2Se_5,[3b] afforded 2-benzyl-4-phenyl-1,3-selenazole (**3a**) in 99% yield (Scheme 1).[7] The oxidation of **3a** with $K_2Cr_2O_7$ in glacial acetic acid gave 2-benzoyl-4-phenyl-1,3-selenazole (**4a**). The yield could be improved by the use of SeO_2 in 1,4-dioxane.[8] After several trial experimentations we have found that treatment of an EtOH solution of **4a** with NaOH (reflux) afforded the desired 2-unsubstituted 1,3-selenazole **5a** in 84% yield (58% overall yield from **1a**). In addition, sodium benzoate was formed which was isolated in the form of benzoic acid. During the optimization of the fragmentation reaction, the base, solvent, concentration and reaction time proved important parameters.[9]



Scheme 1 Synthesis of 2-unsubstituted 1,3-selenazole **5a**

The formation of **5a** can be explained by addition of a hydroxide ion to the carbonyl group to give tetrahedral intermediate **A** (Scheme 1). Due to steric hindrance of the aryl groups, a heterolytic fragmentation occurred.[10] The formation of 4-phenyl-1,3-selenazole-2-carboxylic acid was not observed. The regioselectivity of fragmentation can be explained by stabilization of the negative charge in a 1,3-selenazolyl carbanion (by interaction of the electrons with the unoccupied selenium orbitals) and subsequent protonation of the latter by benzoic acid (Figure 1).

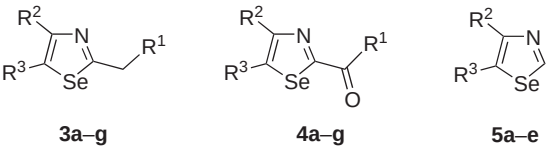


Figure 1

The preparative scope of our methodology was studied. The reaction of α-bromoketones with selenocarboxylic amides afforded the 1,3-selenazoles **3a**–**g**, containing benzyl-, *p*-chlorobenzyl- and *p*-nitrobenzyl groups at carbon C-2, in 60–100% yields (Table 1). The oxidation of **3a**–**g** afforded the 2-benzoyl-1,3-selenazoles **4a**–**g**. In most cases the yields were significantly higher when SeO_2 rather than $K_2Cr_2O_7$ was used.

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Table 1 Synthesis of 1,3-Selenazoles **3a–g** and **4a–g**

3,4	R^1	R^2	R^3	% (**3**)[a]	% (**4**)[a]	
					i[b]	ii[b]
a	C_6H_5	C_6H_5	H	99	64	70
b	C_6H_5	4-Me(C_6H_4)	H	77	–	74
c	C_6H_5	4-Br(C_6H_4)	H	100	60	80
d	C_6H_5	4-NO_2(C_6H_4)	H	88	76	70
e	C_6H_5	C_6H_5	C_6H_5	88	70	–
f	4-Cl(C_6H_4)	C_6H_5	H	60	45	84
g	4-NO_2(C_6H_4)	C_6H_5	H	78	53	72

[a] Isolated yields.
[b] i: $K_2Cr_2O_7$, HOAc; ii: SeO_2, 1,4-dioxane.

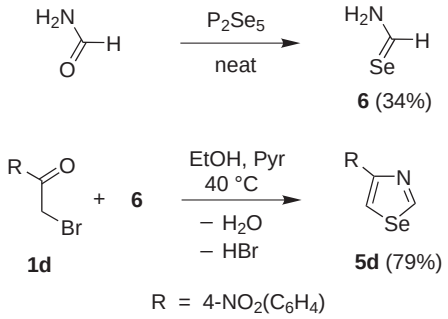
The NaOH/EtOH mediated fragmentation of 2-benzoyl-1,3-selenazoles **4a–e** ($R^1 = C_6H_5$) afforded the 2-unsubstituted 1,3-selenazoles **5a–e** in 71–90% yields (Table 2). The effect of R^1 on the yield was next studied. The best yields of **5a** (84%) were obtained when **4a** or **4g** was used as the starting materials [$R^1 = C_6H_5$, 4-NO_2(C_6H_4)]. The use of chloro derivative **4f** was less efficient. For protons 2-H, low field resonances in the range of δ = 10.13 (**5e**) –10.23 (**5d**) ppm were observed (DMSO-d_6).

Some years ago some of us reported the synthesis of selenoformamide (**6**) by reaction of neat formamide with P_2Se_5.[11a,12] Herein, we wish to report the application of this interesting small molecule to the synthesis of 1,3-selenazoles.[11b] The cyclization of α-bromoketones with **6** provided an independent and useful approach to 2-unsubstituted 1,3-selenazoles: The reaction of **1d** with **6** afforded 1,3-selenazole **5d** in 79% yield (Scheme 2).[13] The advantage of this methodology lies in the fact that only two rather than four synthetic steps are required.

Table 2 Synthesis of 2-Unsubstituted 1,3-Selenazoles **5a–e**

Educt	**5**	R^2	R^3	%[a]	2-*H*[b]	5-*H*[b]
4a	**a**	C_6H_5	H	84	10.16	8.69
4f	**a**	C_6H_5	H	60	10.16	8.69
4g	**a**	C_6H_5	H	84	10.16	8.69
4b	**b**	4-Me(C_6H_4)	H	90	10.15	8.60
4c	**c**	4-Br(C_6H_4)	H	83	10.15	8.76
4d	**d**	4-NO_2(C_6H_4)	H	71	10.23	9.06
4e	**e**	C_6H_5	C_6H_5	77	10.13[c]	–

[a] Isolated yields.
[b] ^{1}H NMR (DMSO-d_6) [ppm].
[c] $CDCl_3$: 9.86 ppm.



Scheme 2 Cyclization of selenoformamide with α-bromoketone **1d**

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(7) **Synthesis of 2-Benzyl-4-phenyl-1,3-selenazole(3a). Typical Procedure.** An EtOH solution (20 mL) of α-bromoacetophenone (0.20 g, 1.0 mmol) and phenylselenoacetic amide (0.20 g, 1.0 mmol) was refluxed for 5 min. After cooling to 20 °C the precipitate was filtered off and recrystallized from EtOH to give **3a** as colourless needles

(0.29 g, 99%), mp 99.5–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.34 (s, 2 H, CH_2), 7.31–7.90 (m, 10 H, Ar), 7.96 [s, 1 H, ^2J (SeH) = 51.3 Hz, 5-H, selenazole]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.28, 118.86 [C-5, ^1J (C_5Se) = 106.6 Hz], 126.62, 127.33, 127.75, 128.70, 128.87, 129.27, 135.51, 138.34, 155.78, 177.95. ^{77}Se NMR ($CDCl_3$, 60% Me_2Se in $CDCl_3$): δ = 738.79. IR (KBr): 1042 (s), 1125 (s), 1320 (w), 1420 (m), 1465 (m), 1520 (s), 3050 (w), 3080 (w) cm^{-1}. MS (70 eV): *m*/*z* (%) = 298 (68) [M$^+$], 182 (100), 102 (93). Anal. Calcd for $C_{16}H_{13}NSe$ (298.25): C, 64.44; H, 4.39; N, 4.70. Found: C, 6.40; H, 4.20; N, 4.79. All products gave correct spectroscopic data and correct elemental analyses and/or high resolution mass data.

(8) **Synthesis of 2-Benzoyl-4-phenyl-1,3-selenazole (4a). Typical Procedure.** To a dioxane solution (20 mL) of **3a** (1.49 g, 5.0 mmol) was added SeO_2 (0.55 g, 5.0 mmol) with stirring. The mixture was heated in a water bath at 40 °C for 3 h. The hot solution was subsequently filtered, cooled, and poured into ice water (50 mL). The crystalline precipitate was filtered off, washed (H_2O), dried in vacuo and recrystallized (EtOH) to give **4a** as yellow needles (1.09 g, 70%), mp 76–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–8.62 (m, 10 H, ArH), 8.54 [s, 1 H, ^2J (SeH) = 50 Hz, 5-H, selenazole]. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.71, 126.77, 128.43, 128.93, 131.45, 133.63, 134.53, 134.92, 158.70, 175.08, 184.67. ^{77}Se NMR ($CDCl_3$, 60% Me_2Se in $CDCl_3$): δ = 807.31. IR (KBr): 840 (m), 901 (m), 1025 (w), 1050 (w), 1075 (w), 1110 (w), 1190 (m), 1270 (s), 1298 (s), 1430 (s), 1465 (s), 1505 (s) cm^{-1}. MS (70 eV): *m*/*z* (%) = 312 (24) [M$^+$], 299 (3), 285 (2), 182 (10), 105 (100), 102 (17), 77 (63), 51 (16), 28 (14). Anal. Calcd for $C_{16}H_{11}NOSe$ (312.22): C, 61.55; H, 3.55; N, 4.49. Found: C, 61.80; H, 3.90; N, 4.29.

(9) **Synthesis of 4,5-Diphenyl-1,3-selenazole (5e). Typical Procedure.** An EtOH solution (30 mL) of 2-benzoyl-4,5-diphenyl-1,3-selenazole (**4e**) (1.65 g, 5 mmol) and NaOH (0.40 g, 10 mmol) was refluxed for 1 h. After cooling, the sodium benzoate formed was filtered off and the solution was poured into ice water. The product was filtered off, dried in vacuo (P_4O_{10}) and recrystallized from petroleum ether to give **5e** as beige needles (0.93 g, 77%), mp 73–74 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.30–7.56 (m, 10 H, ArH), 9.86 [s, 1 H, ^2J (SeH) = 57.26 Hz, 2-H, selenazole]. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 127.59, 128.0, 128.34, 128.66, 129.35, 129.84, 133.96. ^{77}Se NMR ($CDCl_3$, 60% Me_2Se in $CDCl_3$): δ = 806.24, 135.25,149.18, 150.85, 156.78. IR (KBr): 875 (m), 1080 (w), 1190 (w), 1270 (w), 1445 (s), 1495 (m), 1502 (m), 1605 (m), 3080 (m)cm^{-1}. MS (70 eV): *m*/*z* (%) = 285 (60) [M$^+$], 257 (13), 204 (15) , 178 (100). Anal. Calcd for $C_{15}H_{11}NSe$ (284.22): C, 63.21; H, 3.90; N, 4.93. Found: C, 63.21; H, 3.94; N, 4.93.

(10) 2-Unsubstituted 1,3-thiazoles have been prepared by decarboxylation of 1,3-thiazolyl-2-carboxylic acids; see for example: (a) Sarodnick, G.; Kempter, G. *Pharmazie* **1983**, *38*, 829. (b) Pirotte, B.; Delarge, J. *J. Chem. Res., Miniprint* **1990**, *7*, 1634. (c) Strehlke, P. *Chem. Ber*. **1973**, *106*, 721. (d) Sarodnick, G.; Kempter, G. *Z. Chem.* **1979**, *19*, 21.

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(12) **Synthesis of Selenoformamide.**[11a] To freshly prepared P_2Se_5 (114.18 g, 250 mmol, see ref.[3b]) was added destilled formamide (37.16 g, 825 mmol). The reaction mixture was stirred at 60 °C for 5 h and was subsequently extracted with dry Et_2O for 8 h using a Soxhlet apparatus. The Et_2O solution of the extract was collected and the precipitated oil was separated, filtered (to remove precipitated selenium) and dried in vacuo. The oil solidified upon standing in the refrigerator. The solid was recrystallized from Et_2O to give **6** as yellow needles, mp 35–37 °C. IR (KBr): 980 (m), 1095 (m), 1170 (m), 1305 (s), 1375 (s), 1415 (s), 1610 (s), 1680 (s), 2330 (w), 2780 (w), 3300 (s, br) cm^{-1}. Anal. Calcd for CH_3NSe: C, 11.11; H, 2.80; N, 13.02. Found: C, 11.40; H, 3.10; N, 13.11. The solidification of **6** can be achieved only for crude products of good purity. Decomposition of selenoformamide (**6**) occurred upon standing at 20 °C. However, it can be stored at –20 °C for several days. Freshly prepared material should be used for reactions.

(13) **Cyclization of 6 with 1d.** To an EtOH solution of **6** (1.1 g, 10 mmol) was added **1d** (2.4 g, 10 mmol) and pyridine (0.79 g, 10 mmol). The solution was gently warmed, the precipitate formed was filtered off and the filtrate was concentrated. The product precipitated upon standing of the solution at 0 °C and was recrystallized from dry *i*-PrOH or EtOH to give **5d** as slight yellow needles (2.00 g, 79%), mp 160–162 °C.