Synthesis of Primary Selenocarboxamides and Conversion of Alkyl Selenocarboxamides *into* Selenazoles

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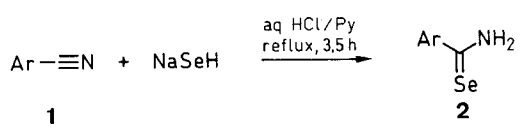
Nitriles react with sodium hydrogen selenide, pyridine and hydrochloric acid in ethanol to give primary aryl and alkyl selenocarboxamides. The alkyl selenocarboxamides are converted into selenazoles by reaction with phenacyl bromide.

There are only a few publications dealing with the synthesis of primary selenocarboxamides. Selenium is almost invariably introduced using hydrogen selenide which is allowed to react with a nitrile.[1] Recently an improved method for the preparation of aryl selenocarboxamides has been reported by Cohen[2] involving the reaction of nitriles with aluminum selenide in boiling water or ethanol. Alkyl selenocarboxamides have also been prepared by Sonoda and co-workers[3] by the reaction of nitriles with selenium, carbon monoxide and water under pressure.

In the course of our investigations on the synthesis of selenium-containing heterocycles, various kinds of primary selenocarboxamides were needed. We now report a one-pot synthesis of primary selenocarboxamides which avoids the use of hydrogen selenide and the high cost or inconvenience of preparation of its precursor, aluminum selenide. The reaction is carried out at atmospheric pressure and primary selenocarboxamides are obtained in good yield. The reaction can conveniently be carried out on a 200 mmol or larger scale.

Ethanolic sodium hydrogen selenide was prepared by reduction of selenium with sodium borohydride according to the method of Klaymann and Shine[4] and the solution was allowed to react with the aryl nitriles **1** under nitrogen in the presence of pyridine and hydrochloric acid, yielding the aryl selenocarboxamides **2a–g**.

This method has also been applied successfully to the preparation of compounds **2h** and **2i**, and alkyl selenocarboxamides **3**. However, owing to the instability of alkyl selenocarboxamides and the difficulty of purifying compounds **2h** and **2i**, these compounds were characterized by their reaction with phenacyl bromide, leading to the corresponding selenazoles. Selenazoles **4a–e** and **4g** which crystallize with difficulty and partially decompose on distillation in vacuo were converted into the corresponding perchlorate salts **5** for characterization.



1 **2**

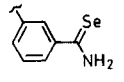
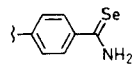
2	Ar	2	Ar
a	Ph	**f**	
b	4-ClC_6H_4		
c	4-MeC_6H_4	**g**	
d	4-$MeOC_6H_4$		
e	3,4-$(MeO)_2C_6H_3$	**h**	
		i	

Table 1. Synthesis of Aryl Selenocarboxamides (**2a–g**)

Compound[a]	Crystallization Solvent	Yield (%)	mp (°C)	Lit.[2] mp (°C)
2a	CH_2Cl_2/benzene (1 : 1)	91.5[a]	122–123	125
2b	benzene	93[b]	124–125	129
2c	toluene	90.5[a]	180–182	186
2c	toluene	84[b]	180–182	186
2d	benzene	74[c]	152–153	157
2e	MeCN	88[c]	177–179[d]	
2f	MeCN	67[b]	164–166[d]	
2g	MeCN/MeOH (1 : 1)	76[a]	156–157[d]	

[a] 50 mmol nitrile. [c] 80 mmol nitrile.
[b] 100 mmol nitrile. [d] New compound.

Table 2. NMR Data of Compounds (**2e–g**)

Compound[a]	^1H NMR, δ[b]	^{13}C NMR, δ[b]
2e	3.80 (6H, s, 2MeO), 6.95–7.70 (3H, m, H_{arom}), 10.08 (1H, b, NH), 10.53 (1H, b, NH)	55.89, 56.04 (2MeO), 110.17, 111.54, 122.44, 133.99, 147.82, 152.12 (C_{arom}), 202.17 (C=Se)
2f	7.32–9.10 (4H, m, H_{arom}), 10.31 (1H, b, NH), 10.76 (1H, b, NH)	121.48, 133.77, 136.83, 146.18, 149.86 (C_{arom}), 202.67 (C=Se)
2g	7.35–8.27 (4H, m, H_{arom}), 10.29 (1H, b, NH), 10.91 (1H, b, NH)	126.02, 128.02, 129.97, 142.62 (C_{arom}), 203.65 (C=Se)

[a] New compounds, satisfactory microanalyses obtained: C ± 0.14, H ± 0.11, N ± 0.10.
[b] Compounds **2e,g** were dissolved in DMSO-d_6, **2f** in DMSO-d_6/$CDCl_3$ (3 : 1).

All reactions were carried out under N_2. The nitriles are commercially available materials and were used without further purification. Melting points were obtained on a Reichert micro hot stage apparatus and are uncorrected. ^1H and ^{13}CNMR spectra were obtained with a Brucker AC-200 spectrometer operating at 200.13 MHz and 50.32 MHz, respectively. For the ^1HNMR spectra TMS was used as internal standard and for the ^{13}CNMR spectra the central $CHCl_3$ peak (δ = 77.00) was used as reference.

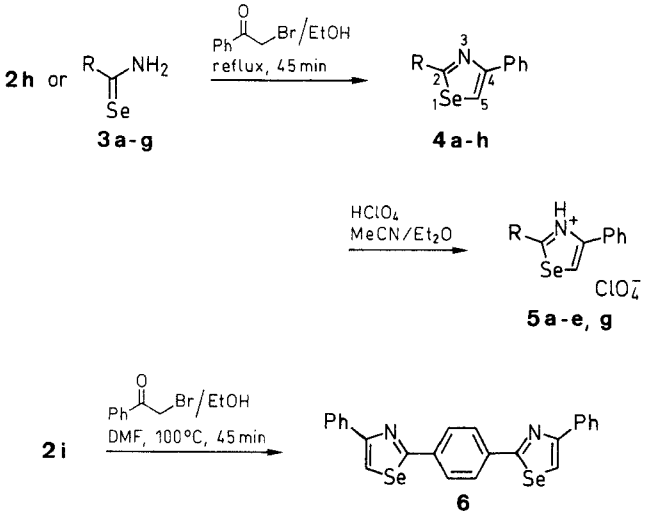
Aryl Selenocarboxamides 2a–g; General Procedure:

$NaBH_4$ (8.1 g, 215 mmol) was added portionwise over 1 h to a suspension of selenium powder (15.8 g, 200 mmol) in EtOH

Table 3. NMR Data and Yields of Selenazoles **4,6**

Compound	Yield[a] (%)	^{1}H NMR ($CDCl_3$), δ, J (Hz)	^{13}C NMR ($CDCl_3$), δ
4a	32.8[b]	1.33 (3H, t, J_{CH_3,CH_2} = 7.46, Me), 2.98 (2H, q, J_{CH_3,CH_2} = 7.46, CH_2), 7.19–7.37 + 7.83–7.88 (6H, m, H_{arom})	14.43 (Me), 30.29 (CH_2), 117.33 (C-5), 126.29, 127.31, 128.33, 135.20 (C_{arom}), 154.90 (C-4), 179.14 (C-2)
4b	46.8[b]	1.03 (3H, t, J_{CH_3,CH_2} = 7.39, Me), 1.74–1.92 (2H, m, CH_2), 3.01 (2H, t, J_{CH_2,CH_2} = 7.85, CH_2), 7.23–7.41 + 7.79–8.02 (6H, m, H_{arom})	13.37 (Me), 23.85 (CH_2), 39.00 (CH_2), 117.57 (C-5), 126.52, 127.53, 128.54, 135.42 (C_{arom}), 155.16 (C-4), 177.83 (C-2)
4c	14.2[b]	1.40 (6H, d, J = 6.82, 2Me), 3.31 (1H, sept, CH), 7.23–7.40 + 7.78–8.02 (6H, m, H_{arom})	23.67 (2Me), 36.53 (CH), 116.99 (C-5), 126.52, 127.51, 128.54, 135.56 (C_{arom}), 155.08 (C-4), 185.05 (C-2)
4d	44.3[b]	1.03–1.41 (4H, $2CH_2$), 2.30–2.45 (1H, m, CH), 7.17–7.41 + 7.65–7.94 (6H, m, H_{arom})	12.16 ($2CH_2$), 18.20 (CH), 115.6 (C-5), 126.47, 127.56, 128.50, 135.36 (C_{arom}), 155.01 (C-4), 180.12 (C-2)
4e	24.7[c]	1.45 (9H, s, t-Bu), 7.21–7.41 + 7.87–7.93 (6H, m, H_{arom})	31.25 (3Me), 40.65 (C), 117.12 (C-5), 126.00, 127.53, 128.61, 135.77 (C_{arom}), 155.04 (C-4), 180.01 (C-2)
4f	32.8[b]	4.31 (2H, s, CH_2), 7.26–7.41 + 7.86–7.91 (11H, m, H_{arom})	43.17 (CH_2), 118.80 (C-5), 126.52, 127.23, 127.65, 128.60, 128.77, 129.17, 135.40, 138.23 (C_{arom}), 155.63 (C-4), 177.80 (C-2)
4g	30.4[b]	3.00 (2H, t, J_{CH_2,CH_2} = 8.06 Hz, CH_2), 3.21 (2H, t, J_{CH_2,CH_2} = 7.96 Hz, CH_2), 7.05–7.33 + 7.59–7.89 (11H, m, H_{arom})	35.52 (CH_2), 38.13 (CH_2), 117.75 (C-5), 125.92, 126.25, 127.28, 127.87, 128.22, 128.30, 135.05, 139.78 (C_{arom}), 154.66 (C-4), 175.70 (C-2)
4h	14.1[b,d]	7.20–7.41 + 7.83–8.07 (13H, m, H_{arom})	117.12 (C-5), 124.82, 126.58, 127.06, 127.85, 128.64, 128.81, 128.88, 135.16, 135.64, 135.79 (C of CH=CH and C_{arom}), 156.68 (C-4), 172.52 (C-2)
6	35.3[b,e]	7.33–7.52 + 7.97–8.20 + 8.59 (14H, m, H_{arom})	120.30 (C-5), 125.83, 126.69, 127.02, 127.89, 134.42, 136.77 (C_{arom}), 155.73 (C-4), 171.59 (C-2)

[a] Yield is calculated on the basis of the nitrile.
[b] 100 mmol nitrile.
[c] 50 mmol nitrile.
[d] In addition to compound **4h**, compound **4g** was isolated in 8.65% yield.
[e] NMR Spectra were obtained in DMSO-d_6 at 113°C.



3–5	R	3–5	R
a	Et	**e**	t-Bu
b	Pr	**f**	$PhCH_2$
c	i-Pr	**g**	$Ph(CH_2)_2$
d		**h**	

(200 mL) under N_2 while H_2 evolved vigorously. The resulting solution was stirred for further 15 min. Pyridine (32.4 mL, 400 mmol) and the aryl nitrile (50–100 mmol; see Table 1) were then added and the solution was heated under reflux while HCl (2 M, 100 mL) was added dropwise over 3 h. The resulting solution was refluxed for an additional 30 min, then filtered while hot. The filtrate was processed according to one of the following procedures (A) or (B).

Table 4. Selenazoles and Selenazolium Perchlorates

Compound[a]	Crystallization Solvent	mp (°C)	Compound[a]	Crystallization Solvent	mp (°C)
4f	MeCN	96–97	**5d**	MeCN/Et_2O (1 : 3)	142–143
4h	MeCN	127–129	**5e**	MeCN/Et_2O (1 : 3)	161–162
5a	MeCN/Et_2O (1 : 3)	166–167	**5g**	MeCN/Et_2O (1 : 3)	141–142
5b	MeCN/Et_2O (1 : 3)	109–110	**6**	CH_2Cl_2	195–197
5c	MeCN/Et_2O (1 : 3)	151–152			

[a] New compounds, satisfactory microanalyses obtained: C ± 0.28, H ± 0.26, N ± 0.24; for **4f**: Se – 0.23.

(A) The filtrate was allowed to stand at r.t. for 2 h. The aryl selenocarboxamide which had precipitated was filtered off, washed with H_2O (2 × 10 mL), then EtOH (2 × 10 mL), dried and recrystallized. Compound **2e** was prepared by this method.

(B) The filtrate was allowed to stand at r.t. for 2 h and a small amount of impurity which had precipitated was filtered off and discarded. The filtrate was added to H_2O (200 mL), the resulting mixture was extracted with CH_2Cl_2 (2 × 300 mL) and the combined extracts were dried (Na_2SO_4). Solvent was removed at reduced pressure. Benzene was then added to give the crude **2** which were then recrystallized. Compounds **2a–d,f,g** were thus prepared.

(*E*)-3-Phenyl-2-propeneselenamide (2h) and the Corresponding 4-Phenyl-2-[(*E*)-2-phenylvinyl]selenazole (4h):

Pyridine (32.4 mL, 400 mmol) and cinnamonitrile (10.05 mL, 80 mmol) were added to a solution of NaSeH under N_2 which had

been prepared from selenium (15.8 g, 200 mmol) and $NaBH_4$ (8.1 g, 215 mmol) in EtOH (200 mL). The resulting solution was heated under reflux while aq HCl (2 M, 100 mL) was added dropwise over 4 h. The solution was refluxed for an additional hour, then allowed to cool to r.t. To this solution sat. aq Na_2CO_3 (100 mL) and then H_2O (200 mL) were added and the resulting solution was extracted with CH_2Cl_2 (4 × 150 mL). The combined extracts were dried (Na_2SO_4), and solvent was removed at reduced pressure. The residue which contained the crude selenocarboxamide was weighed and then dissolved in EtOH (100 mL), and phenacyl bromide (~ 1 equiv, 14 g, 70.3 mmol) was added. The mixture was heated under reflux for 45 min. The solution was then allowed to stand at r.t. for 2 h. A solid (A) which had precipitated was filtered off, washed with Et_2O (2 × 10 mL), dried and weighed (3.78 g), then added to sat. aq Na_2CO_3, and the resulting mixture was extracted with CH_2Cl_2 (2 × 75 mL). The combined extracts were dried (Na_2SO_4) then evaporated at reduced pressure. The residue was recrystallized from MeCN to give the selenazole **4h** (2.2 g). The filtrate obtained after removal of solid A was added to sat. aq Na_2CO_3 (50 mL), and the resulting solution was extracted with CH_2Cl_2 (2 × 150 mL). The combined extracts were dried (Na_2SO_4) and solvent was removed at reduced pressure. A solution of the residue in CH_2Cl_2 (10 mL) was chromatographed on a column of silica gel (30 × 2.0 cm). Elution with benzene/hexane (1:1) gave homogeneous eluates (200 mL) which were evaporated at reduced pressure, and the residue was recrystallized from MeCN to give compound **4h** (1.01 g). The filtrate was evaporated to dryness at reduced pressure, and the residue was chromatographed on a column of silica gel (80 × 2.0 cm). Elution with benzene/CH_2Cl_2 (2:3) gave eluates (200 mL) which yielded more of compound **4h** (0.27 g). The total yield of compound **4h** was 14.1% (3.5 g). Continued elution with benzene/CH_2Cl_2 (2:3) gave eluates (700 mL) which yielded compound **4g** (2.15 g, 8.65%). This compound was found to be identical with the product obtained by the reaction of 3-phenylpropionitrile with NaSeH followed by treatment of the resulting product with phenacyl bromide.

1,4-Benzenedicarboselenoamide (2i) and the Corresponding 1,4-Bis(4-phenyl-2-selenazolyl)benzene (6):

Pyridine (32.4 mL, 400 mmol) and terephthalonitrile (6.4 g, 50 mmol) were added to a solution of NaSeH under N_2 which had been prepared from selenium (15.8 g, 200 mmol) and $NaBH_4$ (8.1 g, 215 mmol) in EtOH (200 mL). The resulting solution was heated under reflux while aq HCl (2 M, 100 mL) was added dropwise over 4 h. The solution was refluxed for an additional 30 min, then allowed to cool to r.t. Solid (14.3 g) which had precipitated was filtered off, washed with H_2O (20 mL), then MeCN (10 mL × 2) and dried under vacuum (0.2 Torr). This solid and phenacyl bromide (20 g, 100 mmol) were placed in a solution of DMF (20 mL) and EtOH (100 mL), and the resulting mixture was stirred in an oil bath (100 °C) for 45 min. The mixture was allowed to cool to r.t., then poured into sat. aq Na_2CO_3 (200 mL). The resulting mixture was extracted with CH_2Cl_2 (6 × 350 mL), the combined extracts were dried (Na_2SO_4), and solvent was removed at reduced pressure. The residue was recrystallized from CH_2Cl_2 (addition of hexane) to give compound **6**.

Alkyl Selenocarboxamides 3 and the Corresponding Selenazoles 4; General Procedure:

Pyridine (32.4 mL, 400 mmol) and the alkyl nitrile (50–100 mmol; see Table 3) were added to a solution of NaSeH under N_2 which had been prepared from selenium (15.8 g, 200 mmol) and $NaBH_4$ (8.1 g, 215 mmol) in EtOH (200 mL). The resulting solution was heated under reflux while HCl (2 M, 100 mL) was added dropwise over 4 h. The resulting solution was refluxed for an additional 30 min, then allowed to cool to r.t. Sat. aq Na_2CO_3 (100 mL) and H_2O (200 mL) were added and the resulting solution was extracted with CH_2Cl_2 (4 × 150 mL). The combined extracts were dried (Na_2SO_4), and solvent was removed at reduced pressure. The residue which contained the crude **3** was weighed, dissolved in EtOH (50 mL), and phenacyl bromide (~ 1 equiv) was added. The mixture was then heated under reflux for 45 min, solvent was removed at reduced pressure, and Et_2O was then added. The salt which had precipitated was filtered off, washed with Et_2O (20 mL) and dried. HBr in AcOH [2 mL, 33% (w/w)] was added to the filtrate to give a second crop of the salt. The combined crops were dissolved in EtOH (50 mL) and sat. aq Na_2CO_3 (50 mL) was added. The resulting solution was extracted with CH_2Cl_2 (2 × 100 mL) and the combined extracts were dried (Na_2SO_4), then solvent was removed at reduced pressure. A solution of the residue in CH_2Cl_2 (15 mL) was chromatographed on a column of silica gel (30 × 2.0 cm). Elution with benzene/hexane (1:1) gave homogeneous eluates (250 mL). Solvent was removed from the eluates completely under vacuum (10 Torr). The yield of selenazole was calculated on the crude material if it could not be recrystallized. Selenazoles **4a–g** were thus prepared.

Conversion of Selenazoles into Selenazolium Perchlorates:

The selenazoles **4a–e,g**, all of which have low melting points, were converted into the perchlorates **5a–e,g** for characterization as follows.

The selenazole (2 mmol) was dissolved in MeCN (2 mL) and a 40% excess of $HClO_4$ [0.24 mL, 70% (w/w)] in MeCN (2 mL) was then added. Et_2O (40 mL) was added to the resulting solution, and the salt which precipitated as colorless plates was filtered off, washed with Et_2O (2 × 2 mL) and dried. Yields: **5a**: 89%; **5b**: 77%; **5c**: 78%; **5d**: 73%; **5e**; 91.5%; **5g**: 76%.

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