Efficient Synthesis of Primary Selenocarboxylic Amides by Reaction of Nitriles with Phosphorous(V) Selenide

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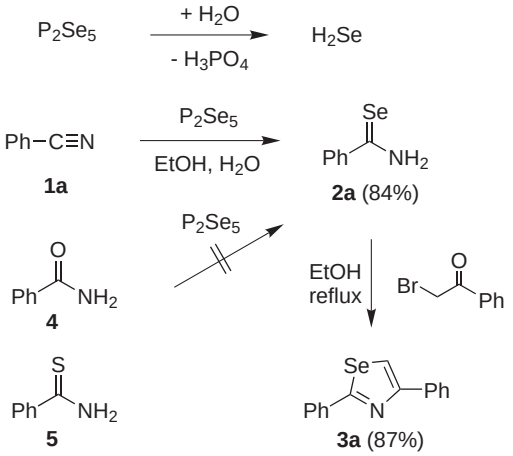
Abstract: The reaction of nitriles with P_2Se_5 in the presence of EtOH/H_2O afforded a variety of primary selenocarboxylic amides.

Key words: cyclizations, heterocycles, nitriles, selenium, synthetic methodology

Selenium containing heterocycles are of considerable current interest, due to their pharmacological activity. A prominent example is the antitumor and antiviral active C-glycosyl selenazole selenazofurin.[1] In contrast to their sulfur analogues, there exist only limited methods for the synthesis of *N*,*Se*-heterocycles, e. g. 1,3-selenazoles.[2] Many syntheses rely on the use of primary seleno-ureas and selenocarboxylic amides. However, these important building blocks are not readily available and there are many drawbacks of known synthetic procedures. Selenocarboxylic amides have been prepared by reaction of nitriles with H_2Se, NaSeH,[3a] generated by $NaBH_4$/Se,[3] by use of Se/CO,[4] and tris(trimethylsilyl)-monoselenophosphate.[5] These methods are restricted mainly to aryl substituted derivatives or require toxic or not readily available reagents. An alternative synthesis of selenocarboxylic amides relies on the reaction of nitriles with Al_2Se_3 in the presence of Et_3N/pyridine/H_2O.[6] Unfortunately, many yields given in this paper could not be reproduced in our hands (vide infra).[7]

Herein, we wish to report a new method for the synthesis of primary selenocarboxylic amides by reaction of nitriles with P_2Se_5 in the presence of EtOH/H_2O (Scheme 1). From a preparative viewpoint, our methodology is more convenient and reliable than the use of Al_2Se_3 and is less toxic than CO, NaSeH or H_2Se. In addition, P_2Se_5 is much easier and more reliably available in pure form and is less prone to hydrolysis than Al_2Se_3. It can be handled in presence of air and stored for a long time under inert atmosphere.[7] Our methodology allows the preparation of a great variety of selenocarboxylic amides. The yields obtained for known products are in many cases better than those reported for other methods. In addition, a number of novel functionalized derivatives were prepared with good chemoselectivity. The selenocarboxylic amides prepared represent versatile synthetic building blocks and were



Scheme 1 Synthesis of selenocarboxylic amides by reaction of nitriles with P_2Se_5

transformed into 1,3-selenazoles by reaction with α-bromoketones.

Our initial attempts to prepare primary selenocarboxylic amides by reaction of carboxylic amides with P_2Se_5 were unsuccessful under a variety of conditions (variation of the stoichiometry, solvent, temperature, reaction time and additives such as HCl, NaOH, Ph_3P or PCl_3).[8,9] We have eventually found that primary selenocarboxylic amides can be prepared in good yields by reaction of nitriles with P_2Se_5.[10] Slow addition of water to the reaction mixture resulted in formation of small amounts of hydrogen selenide in situ which subsequently added to the nitrile. During the optimization of the reaction the following parameters proved important (Table 1): a) use of 0.4 equivalents of P_2Se_5 (corresponding to 2.0 equiv of selenium), b) *slow* addition of water or P_2Se_5 to the reaction mixture, c) use of EtOH/H_2O, d) reaction time and temperature, e) crystallization solvent (Table 2). An attempt to directly use a mixture of the elements (P/Se = 2:5) rather than P_2Se_5 proved unsuccessful. The cyclization of **2a** with α-bromoacetophenone afforded 1,3-selenazole **3a** in 87% yield.[11]

In order to study the preparative scope of our methodology, the substituents of the nitrile were systematically varied (Scheme 2, Table 2). The reaction of benzonitrile and 2-tolylnitrile with P_2Se_5 afforded selenocarboxylic amides **2a** and **2b**, respectively. Starting with acetonitrile

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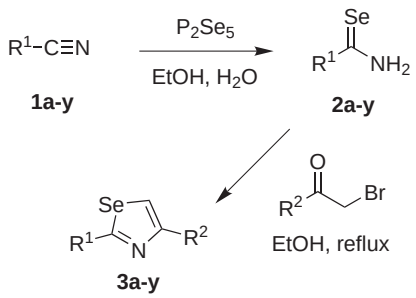
Table 1 Optimization of the Synthesis of **2a**

Entry	Educt	Reagent	Equiv	Additive	*t* (h)	Temp.	(%)[a]
1	**1a**	Al_2Se_3	1.4	NEt_3/pyridine/H_2O	2	reflux	49
2	**1a**	P_2Se_5	0.4	NEt_3/pyridine/H_2O	2	reflux	72
3	**1a**	P_2Se_5	0.4	EtOH/H_2O	2	reflux	84
4	**1a**	P_2Se_5	0.2	EtOH/H_2O	2	reflux	55
5	**4**	P_2Se_5	0.4	[b]	2	reflux	0
6	**5**	P_2Se_5	0.4	[b]	2	reflux	0
7	**1a**	P/Se[c]	0.4	EtOH/H_2O	2	reflux	9
8	**1a**	P_2Se_5	0.4	EtOH/H_2O	0.5	reflux	34
9	**1a**	P_2Se_5	0.4	EtOH/H_2O	12	reflux	27
10	**1a**	P_2Se_5	0.4	EtOH/H_2O	12	20 °C	0

[a] Isolated yields.
[b] Various conditions, see text.
[c] Mixture P/Se = 2:5



Scheme 2 Synthesis of selenocarboxylic amides and 1,3-selenazoles

and propionitrile, selenocarboxylic amides **2c** and **2d** were prepared, respectively. Alkyl-substituted derivatives are generally rather unstable and difficult to prepare. Selenocarboxylic amide **2e** was prepared from phenylacetonitrile. The use of Al_2Se_3, following the protocol reported by Cohen,[6] proved unsatisfactory in our hands: selenocarboxylic amides **2a**–**e** were isolated in only 49%, 14%, 7%, 3% and 21% yields, respectively. The reaction of P_2Se_5 with dibenzylacetonitrile afforded selenocarboxylic amide **2f**. Products **2g**–**i** were prepared from pyridyl substituted nitriles. The novel functionalized selenocarboxylic amides **2j**–**m**, containing a nitrile, carboxylic acid, ester and guanidine moiety, were prepared from **1j**–**m** with very good chemoselectivity. A protection of the functional groups was not required. Selenation of malonic dinitrile afforded the novel difunctional derivative **2n**. Phenylethenyl-, *tert*-butyl- and naphthyl-substituted selenocarboxylic amides **2o**–**q** could be prepared from the corresponding nitriles **1o**–**q**. The reaction of P_2Se_5 with functionalized aromatic nitriles afforded products **2r**–**v** with very good chemoselectivity. Seleno-urea (**2x**) and selenoglycin amide (**2y**), which represents to our knowledge the first amino acid derived selenocarboxylic amide, were successfully prepared from cyanamide and aminoacetonitrile, respectively. The cyclization of selenocarboxylic amides **2** with α-bromoketones afforded a variety of 1,3-selenazoles **3** (Scheme 2, Table 2).[11]

We have reported a chemoselective, convenient and reliable synthesis of a variety of selenocarboxylic amides including a number of novel functionalized derivatives. The yields obtained for known products compare well to those reported for other methods. Selenocarboxylic amides represent useful building blocks for the synthesis of 1,3-selenazoles and other pharmacologically relevant *N*/*Se*-heterocycles.

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References

(1) Goldstein, B. M.; Kennedy, S. D.; Hennen, W. J. *J. Am. Chem. Soc.* **1990**, *112*, 8265; and references cited therein.
(2) (a) Larsen, R. In *Comprehensive Heterocyclic Chemistry II*, Vol. 3; Shinkai, I., Ed.; Elsevier Science: Oxford, **1996**, Chap. 8. (b) Wirth, T. *Organoselenium Chemistry, Modern Developments in Organic Synthesis*; Springer: Berlin, **2000**. (c) Koketsu, M.; Nada, F.; Ishihara, H. *Synthesis* **2002**, 195; and references cited therein.

Table 2 Yields of Selenocarboxylic Amides **2** and 1,3-Selenazoles **3**

2/**3**	R^1	Appearance (Crystallization solvent)	Mp (°C)	% (**2**)[a]	R^2	% (**3**)[a]
a	Ph	Golden needles (C_6H_6/PE)	125–126	84	Ph	87
b	2-$(H_3C)C_6H_4$	Yellow needles (C_6H_6/PE)	109–111	30	Ph	93
c	Me	Colorless prisms (C_6H_6)	125–126	27	4-BrC_6H_4	53
d	Et	Colorless prisms (C_6H_6)	56–57	20	Me	61
e	$PhCH_2$	Colorless needles (C_6H_6/PE)	92–93	40	Ph	100
f	Ph_2CH	Yellow prisms (C_6H_6/PE)	148–150	81	H	61
g	2-Pyridyl	Colorless needles (C_6H_6/PE)	143–144	37	Ph	93
h	3-Pyridyl	Golden needles (EtOH)	146–147	18	4-BrC_6H_4	61
i	4-Pyridyl	Orange lamella (DMF/H_2O)	142–143	36	4-BrC_6H_4	81
j	$(NC)CH_2$	Brown needles (EtOH)	108–109	41	–	–
k	$H_2NC(=O)CH_2$	Yellow prisms (EtOH)	120–122	47	Ph	95
l	$(EtO_2C)CH_2$	Colorless liquid	Dec.	33	4-$(O_2N)C_6H_4$	74
m	$H_2NC(=NH)NH$	Grey prisms (EtOH)	162–164	55	–	–
n	$H_2NC(=Se)CH_2$	Yellow needles (DMF/$CHCl_3$)	Dec.	52	–	–
o	PhCH=CH	Colorless liquid	Dec.	42	Me	61
p	*t*Bu	Colorless needles (C_6H_6)	132–133	58	–	–
q	1-Naphthyl	Yellow prisms (EtOH)	130–132	35	Ph	80
r	4-$(H_2N)C_6H_4$	Yellow prisms (EtOH)	127–128	22	Ph	87
s	2-$(HO)C_6H_4$	Yellow lamella (toluene/PE)	106–108	48	H	29
t	4-$(HO)C_6H_4$	Yellow needles (H_2O)	175–176	57	H	25
u	4-$ClC_6H_4CH_2$	Colorless needles (C_6H_6)	94–96	73	4-BrC_6H_4	73
v	4-$(O_2N)C_6H_4CH_2$	Yellow needles (EtOH)	219–221	70	4-$(H_3C)C_6H_4$	86
w	Cyclohexyl	Colorless needles (C_6H_6)	130–133	26	4-BrC_6H_4	54
x	H_2N	Colorless needles (H_2O)	204–206	37	Ph	87
y	$(H_2N)CH_2$[b]	Colorless needles (EtOH)	195–197	59	–	–

[a] Isolated yields of free amide.
[b] Isolated yield of hydrobromide.

(3) (a) Lai, L.-L.; Reid, D. H. *Synthesis* **1993**, 870. (b) Klayman, D. L.; Griffins, T. S. *J. Am. Chem. Soc.* **1973**, *95*, 197. (c) For the use of $LiAlH_4$/Se, see: Ishihara, H.; Koketsu, M.; Fukuta, Y.; Nada, F. *J. Am. Chem. Soc.* **2001**, *123*, 8408. (d) Also see: Koketsu, M.; Fukuta, Y.; Ishihara, H. *Tetrahedron Lett.* **2001**, *42*, 6333.

(4) Ogawa, A.; Miyaka, J.; Karasaki, Y.; Murai, S.; Sonoda, N. *J. Org. Chem.* **1985**, *50*, 384.

(5) Kaminski, R.; Glass, R. S.; Skowronska, A. *Synthesis* **2001**, 1308.

(6) Cohen, V. J. *Synthesis* **1978**, 668.

(7) This can have several reasons: (a) We have found that the aluminothermic formation of Al_2Se_3 from the elements is often not complete and strongly depends on the particle size of aluminum and on many other parameters: Brauer, B. *Handbuch der präparativen anorganischen Chemie*; Ferd. Enke Verlag: Stuttgart, **1960**, 732. (b) It is necessary, but extremely difficult to remove remaining aluminum. In addition, Al_2Se_3 is very prone to hydrolysis and has to be handled with great care (glove box). Since it has to be used as a powder, substantial decomposition readily occurs and impurities cannot be separated.

(8) For the synthesis of thioamides from amides, see: Raucher, S.; Klein, P. *J. Org. Chem.* **1981**, *46*, 3558.

(9) For the synthesis of *N*,*N*-disubstituted selenocarboxylic amides, see: (a) Collhard-Charon, C.; Renson, M. *Bull. Soc. Chim. Belg.* **1963**, *72*, 304. (b) Jensen, K. A.; Nielsen, P. H. *Acta Chim. Scand.* **1966**, *20*, 597. (c) See also: Sukhai, R. S.; de Jong, R.; Brandsma, L. *Synthesis* **1977**, 888.

(10) General procedure for the preparation of selenocarboxylic amides: Method A (for **2a**–**2t**): An ethanol solution (15–30 mL) of the nitrile (50 mmol) and of freshly prepared P_2Se_5 (9.1 g, 20 mmol) was refluxed. Subsequently, water (3–6 mL) was added dropwise during 2–3 h. After cooling, the solution was filtered and water was added to the filtrate which resulted in precipitation of the selenocarboxylic amide **2**. In some cases, the aqueous layer was extracted with ether or benzene. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Cooling (dry ice) or addition of petroleum ether resulted in crystallization of the product. The crude product was dried (desiccator, P_2O_5) and crystallized from the solvent indicated (Table 2).
Method B (for **2u**–**2y**): The nitrile (50 mmol) was dissolved in ethanol (15–30 mL) and water (3–6 mL). To the refluxing solution was added freshly prepared P_2Se_5 (9.1 g, 20 mmol) in small portions during 2–3 h. The solution was cooled and filtered. Water was added to the filtrate which resulted in precipitation of the selenocarboxylic amide **2**. In some cases, the aqueous layer was extracted with benzene. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Cooling (dry ice) or addition of petroleum ether resulted in crystallization of the product. The crude product was dried (exsiccator, P_2O_5) and crystallized from the solvent indicated (Table 2). For **2x**, only water was used as the solvent. In case of **2x** and **2y**, the hot solution was filtered without prior cooling. Concentration of the filtrate resulted in precipitation of the pure product.
Spectroscopic data of 2-methyl-selenobenzamide (**2b**): ^{1}H NMR (C_6D_6, 300 MHz): δ 2.15 (s, 3 H, CH_3), 5.90 (br, 1 H, NH), 6.78–7.22 (m, 4 H, Ar), 8.20 (br, 1 H, NH). ^{13}C NMR (C_6D_6, 75 MHz): δ_c 19.67 (CH_3), 125.67, 125.68, 126.22, 126.24, 128.99, 130.70 (Ar), 210.46 (C=Se). IR (KBr, cm^{-1}): 1620 (s), 1420 (s), 1290 (m), 1265 (w), 1230 (w), 1155 (w), 1130 (w), 1045 (w), 855 (m). MS (70 eV): *m/z* (%): 199 (100, M^+). Anal. calcd. for C_8H_9NSe (198.13): C 48.50, H 4.58, N 7.07, Se 38.86; found C 48.50, H 4.30, N 7.10, Se 39.50. All new compounds gave satisfactory analytical or high resolution mass data.
Synthesis of P_2Se_5: A mixture of red phosphorous and grey selenium powder was heated in a tube with minor Bunsen burner flame until the reaction was complete. The reaction mixture was grounded and powdered to give P_2Se_5 as a grey solid. For comparison, see: Kudchadker, M. V.; Zingaro, R. A.; Irgolic, K. J. *Can. J. Chem.* **1968**, *46*, 1415.

(11) Typical procedure for the preparation of 1,3-selenazoles: An EtOH solution (20 mL) of selenobenzamide (1.84 g, 10 mmol) and α-bromoacetophenone (1.99 g, 10 mmol) was stirred under evolution of heat. After cooling, the mixture was poured into H_2O. The precipitated product was filtered off and recrystallized from EtOH to give **3a** as colorless lamella (2.47 g, 87%).
Spectroscopic data of 2,4-diphenyl-1,3-selenazole (**3a**): mp: 99 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38–8.01 (m, 10 H, Ar), 8.06 (s, 1 H, 5-H). ^2J (SeH) = 58.3 Hz. ^{13}C NMR ($CDCl_3$, 75 MHz): δ_c 118.26, 126.72, 127.08, 127.91, 128.70, 128.97, 130.21, 135.42, 136.41, 156.93, 173.87. ^{77}Se NMR ($CDCl_3$, 100% Me_2Se): δ 712.69 ($^2J_{Se\text{-}H}$ = 58.3 Hz). IR (KBr, cm^{-1}): 3114 (m), 1598 (s), 1509 (s), 1481 (s), 1442 (s), 1279 (m), 1152 (m), 1071 (m), 1043 (s), 1027 (m), 952 (s). MS (70 eV): *m/z* (%): 285 (59, M^+), 182 (100), 102 (86). Anal. calcd. for $C_{15}H_{11}NSe$ (284.22): C 63.39, H 3.90, N 4.93; found C 63.45, H 3.92, N 4.91. All new compounds gave satisfactory analytical or high resolution mass data.