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A Novel Selenium-Containing Heterocycle. Lewis Acid-Assisted Reaction of Selenoamides with Aldehydes Leading to 6*H*-1,3,5-Oxaselenazines

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New selenium-containing heterocyclic compounds, 6*H*-1,3,5-oxaselenazines, have been synthesized stereoselectively by the reaction of selenoamides with aldehydes in the presence of boron trifluoride etherate complex.

Selenoamides hold great promise as useful precursors for synthesis of selenium-nitrogen heterocyclic compounds,[1,2] since they have a highly reactive carbon-selenium double bond as well as an intrinsical Se-C-N unit. Nonetheless, practical use of selenoamides for the synthesis of heterocycles has been limited to some examples[3] owing to the difficulty in preparing selenoamides.[4] Recently, we have developed a convenient method for synthesis of selenoamides by the reaction of nitriles with selenium, carbon monoxide, and water.[5] Herein we report the Lewis acid-assisted condensation of selenoamides with aliphatic aldehydes, leading to novel heterocyclic compounds containing a Se-C-N unit in the ring with high stereoselectivity.[6]

Boron trifluoride etherate complex (10 mmol) was added dropwise over 2-min period to a magnetically stirred mixture of selenobenzamide (5 mmol) and acetaldehyde (12 mmol) in chloroform (20 mL) at 0 °C. The resultant solution was warmed to 20 °C and stirring was continued for 1 h. The reaction mixture was poured

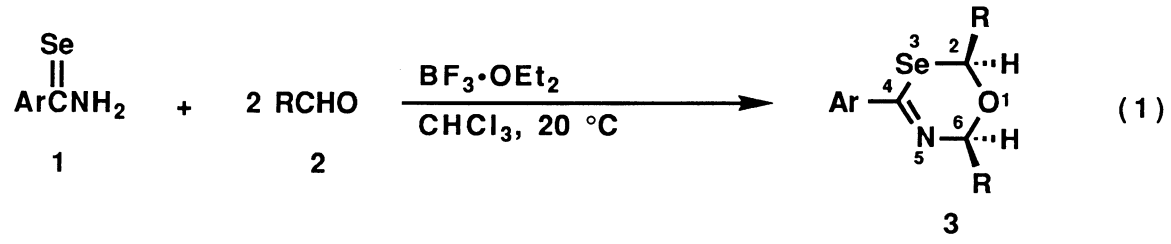

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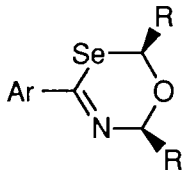
Table 1. Synthesis of 6*H*-1,3,5-Oxaselenazines **3**[a)]

Entry	Selenoamide **1**	Aldehyde **2**	Product **3**	Yield/%[b)]	Mp θ_m/°C
	$ArC(=Se)NH_2$	RCHO			
1	Ar = Ph	R = CH_3	**3a**	82	oil
2	Ar = Ph	R = *n*-C_7H_{15}	**3b**	69	oil
3	Ar = Ph	R = *t*-C_4H_9	**3c**	86	98.0 ~ 98.5
4	Ar = Ph	R = 	**3d**	97	78.0 ~ 79.0
5	Ar = *m*-ClC_6H_4	R = 	**3e**	83	70.0 ~ 71.0
6	Ar = *p*-$CH_3OC_6H_4$	R = 	**3f**	97	80.5 ~ 81.0

a) Reaction time: 20 h except for entries 1 and 2 (1 h). b) Isolated yield of *cis*-isomer.

into 30 mL of saturated aqueous $NaHCO_3$ and extracted with diethyl ether (3 X 20 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residual oil was purified by flash chromatography on silica gel (eluted with hexane/Et_2O = 100/1) to afford 2,6-dimethyl-6*H*-1,3,5-oxaselenazine (**3a**) in 82% yield.

Results are summarized in Table 1. The method is successful with aliphatic aldehydes, and provided oxaselenazines **3** in good yields. In contrast, the reaction of aromatic aldehydes with selenoamides resulted in the formation of a complex mixture with deposition of elemental selenium. As for the Lewis acids, $TiCl_4$ and $AlCl_3$ were less effective than BF_3•OEt_2. $FeCl_3$ and $ZnCl_2$ exerted no effect on this reaction.

Spectral data of oxaselenazines **3** are listed in Table 2. In ^{13}C NMR, the underlined signals can be assigned to the α-carbon of selenium (C2) on the basis of satellite caused by ^{77}Se. By a similar reason, H^a can also be distinguished clearly from H^b in ^1H NMR. In ^{77}Se NMR, the signals of **3** appeared at δ 340 ± 40.[7)]

Isolated oxaselenazines **3** are all single stereoisomers with *cis*-configuration,[8)] which was confirmed by the observed NOE enhancements of the integral of H^a by 7-10% and no increment

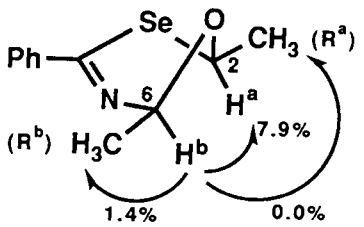
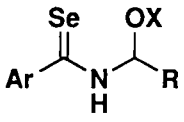


Fig. 1.

Table 2. Spectral Data of Oxaselenazines **3**[a)]

	IR ν/cm^{-1} (νC=N)	MS m/e (CI, M^++1)	^{1}H NMR[b)] δ/ppm	(H^a) (H^b)	^{13}C NMR[c)] δ/ppm (Cn, $^1J_{SeC}$)	^{77}Se NMR[d)] δ/ppm ($^2J_{SeH}$, $^3J_{SeH}$/Hz)
3a	1611 (neat)	255 (M^+)[e)]	5.65 (q, J= 6.1 Hz) 5.17 (q, J= 6.1 Hz)		73.3 (C2, 56.8 Hz) 157.8 (C4), 89.5 (C6)	381 (12.5, 16.3)
3b	1620 (neat)	424	5.59 (dd, J= 5.6, 6.9 Hz) 4.98 (dd, J= 5.4, 6.8 Hz)		78.5 (C2, 56.8 Hz) 157.6 (C4), 92.7 (C6)	362 (11.0, 11.0)
3c	1622 (KBr)	240	5.42 (s) 4.62 (s)		84.2 (C2, 61.0 Hz) 156.6 (C4), 96.1 (C6)	315 (12.6)
3d	1618 (KBr)	392	5.41 (d, J= 7.0 Hz) 4.74 (d, J= 5.2 Hz)		89.0 (C2, 58.6 Hz) 157.9 (C4), 99.0 (C6)	343 (12.6, 6.1)
3e	1615 (KBr)	426	5.41 (d, J= 6.1 Hz) 4.72 (d, J= 5.2 Hz)		84.6 (C2, 59.0 Hz) 157.7 (C4), 96.0 (C6)	348 (12.0, 6.5)
3f	1609 (KBr)	-[f)]	5.39 (d, J= 6.7 Hz) 4.72 (d, J= 5.5 Hz)		84.2 (C2, 59.6 Hz) 161.6 (C4), 96.0 (C6)	336 (12.4, 6.0)

a) All products gave satisfactory analytical data (C ± 0.35, H ± 0.21, N ± 0.18%). b) ^{1}H-^{77}Se couplings were observed for H^a. c) ^{13}C-^{77}Se couplings were observed for C2. d) External Me_2Se (neat) was used as the standard (δ = 0). e) The value for M^+ was obtained by EI. f) The value (M^++1-RCO = 310) was obtained.



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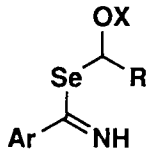

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of the integrated intensity on the protons of R^a, upon irradiation of H^b (see, Fig. 1).[9)]

A possible reaction path may involve the initial formation of **4** (X = Lewis acid) and/or **5** (X = Lewis acid) by the reaction of selenoamides with one equivalent of aldehydes in the presence of BF_3•Et_2O. The reaction of a selenoamide **1** (Ar = Ph) with an aldehyde **2** (R = cyclohexyl) was carried out in a shorter time (10 min) at 0 °C, and quenched immediately with water. After a usual workup, **4** (Ar = Ph, R = cyclohexyl, X = H)[10)] was obtained together with an oxaselenazine **3d,** but **5** (Ar = Ph, R = cyclohexyl, X = H) was not detected. This observation suggests the intermediacy of **4** (X = Lewis acid).

In summary, a new selenium-nitrogen heterocycle **3** was easily synthesized by using selenoamide as the key starting material.

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References

1) A review for selenium-nitrogen heterocycles, see: E. Bulka, *Chem. Scr.*, **8A**, 39 (1975).

2) Recently, some selenium-nitrogen heterocycles were reported to exhibit high antitumor activity, see: P. C. Srivastava and R. K. Robins, *J. Med. Chem.*, **26**, 445 (1983).

3) a) W. Becker and J. Meyer, *Chem. Ber.*, **37**, 2550 (1904); b) K. A. Jensen and U. Henriksen, *Acta Chem. Scand.*, **21**, 1991 (1967); c) M. P. Cava and L. E. Saris, *J. Chem. Soc., Chem. Commun.*, **1975**, 617; d) J. Liebscher and H. Hartmann, *Synthesis*, **1976**, 521; *Tetrahedron*, **33**, 731 (1977); e) V. I. Cohen, *J. Heterocycl. Chem.*, **15**, 1113 (1978); **16**, 365 (1979); *Synthesis*, **1978**, 768; **1979**, 66; f) A. Shafiee, *J. Heterocycl. Chem.*, **15**, 473 (1978); A. Shafiee and S. Sattari, *ibid.*, **19**, 227 (1982); g) W. J. Hennen, B. C. Hinshaw, T. A. Riley, S. G. Wood, and R. K. Robins, *J. Org. Chem.*, **50**, 1741 (1985); h) C. Bochu, A. Couture, and P. Grandclaudon, *ibid.*, **53**, 4852 (1988).

4) Some of the known methods for the synthesis of selenoamides, require the handling of highly toxic and air-sensitive hydrogen selenide, see: K. Kindler, *Liebigs Ann. Chem.*, **431**, 187 (1923) and Ref. 2. High temperature and long reaction time are essential for the preparation from amides and P_2Se_5, see: C. Collard-Charon and M. Renson, *Bull. Soc. Chim. Belg.*, **72**, 304 (1963); I. D. Rae and M. J. Wade, *Int. J. Sulfur Chem.*, **8**, 519 (1976). The methods usable for the synthesis of selenoamides, are as follows: For N-unsubstituted selenoamides, see: V. I. Cohen, *Synthesis*, **1978**, 668. For N-substituted selenoamides, see: F. Malek-Yazdi and M. Yalpani, *ibid.*, **1977**, 328 and Ref. 3c.

5) A. Ogawa, J. Miyake, Y. Karasaki, S. Murai, and N. Sonoda, *J. Org. Chem.*, **50**, 384 (1985); A. Ogawa, J. Miyake, N. Kambe, S. Murai, and N. Sonoda, *Bull. Chem. Soc. Jpn.*, **58**, 1448 (1985).

6) For the sulfur analogue, see: C. Giordano and A. Belli, *Synthesis*, **1975**, 789.

7) The ^{77}Se NMR spectra of **3** were taken on a Brucker AM 600 spectrometer (sweep width = 2000 Hz, 65 K data points, pulse width = 45°, acquisition time = 1.024s).

8) In all cases examined, signals assigned to the *trans*-isomer (<7%) were detected in a crude mixture by ^1H NMR. Isomerization of the *trans*-oxaselenazine into the more stable *cis*-isomer seems to take place during the purification by column chromatography on silica gel.

9) A. Terada and Y. Kishida, *Chem. Pharm. Bull.*, **18**, 497 (1970); M. Yoshimoto and Y. Kishida, *ibid.*, **18**, 2518 (1970); T. Kusumi, D. Muanza-Nkongolo, M. Goya, M. Ishitsuka, T. Iwashita, and H. Kakisawa, *J. Org. Chem.*, **51**, 384 (1986).

10) Spectral data of **4** are as follows: IR (KBr) 3200-3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.12 (d, O<u>H</u>, J_{CHOH} = 3.4 Hz, exchangeable), 5.49 (ddd, NHC<u>H</u>(OH)CH, J_{NHCH} = 6.1, J_{CHOH} = 3.4, J_{CHCH} = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 84.4 (NH<u>C</u>H), 206.1 (<u>C</u>=Se), MS (CI, m/e) 298 (M^++1).

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