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SYNTHESIS OF 1,3-SELENAZETIDINE DERIVATIVES FROM IMINES AND THIOCARBAMOYL ISOSELENOCYANATE

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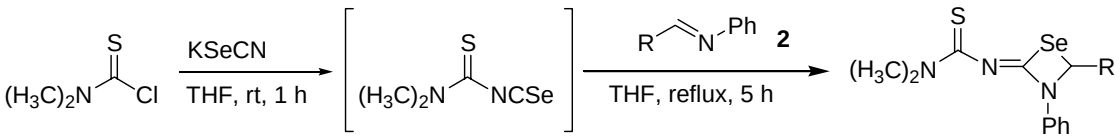
Abstract – Reactions of thiocarbamoyl isoselenocyanate with imines afforded 1,3-selenazetidines under reflux conditions. We could confirm the structure using significant difference of chemical shifts between selenazetidines and selenoureas including cyclic selenoureas in ^{77}Se NMR spectra.

INTRODUCTION

The chemistry of selenium-nitrogen containing heterocycles has attracted much attention because of their reactivity[1] and pharmaceutical applications.[2] In this decade, there are several reports regarding selenium-nitrogen containing five-membered ring, 1,3-selenazole derivatives, and six-membered ring, 1,3-selenazine derivatives,[1] whereas four-membered ring compounds including selenium-nitrogen are little known. There currently exist only three practical syntheses of 1,3-selenazetidines.[3] We describe here a synthesis of 1,3-selenazetidines from thiocarbamoyl isoselenocyanate with imines. We found significant difference of chemical shifts between selenazetidines and selenoureas including cyclic selenoureas in ^{77}Se NMR spectra.

RESULTS AND DISCUSSION

Thiocarbamoyl isoselenocyanate (**1**) was prepared by reactions of thiocarbamoyl chloride with KSeCN.[4] Reactions of the thiocarbamoyl isoselenocyanates (**1**) with imines (**2**) were carried out at reflux in THF for 5 h. The reactions gave 2-imino-1,3-selenazetidines (**3**), formal [2+2] cycloadducts (Scheme 1).



Scheme 1

Table 1. Preparation of 2-Imino-1,3-selenazetidines (**3**)

Entry	R	Yield (%) **3**
1	C_6H_5	32 (**3a**)
2	*p*-$CH_3C_6H_4$	33 (**3b**)
3	*p*-ClC_6H_4	10 (**3c**)
4	*p*-$(CH_3)_2CHC_6H_4$	20 (**3d**)

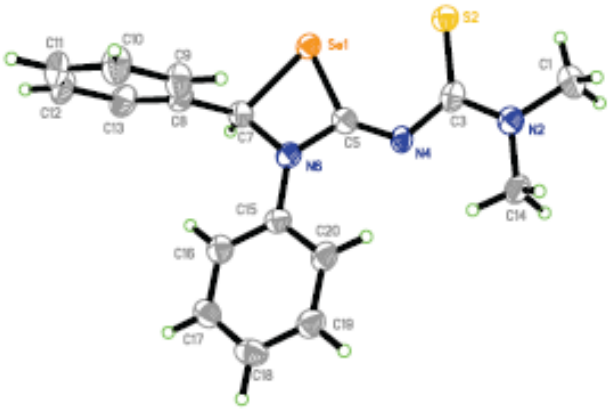
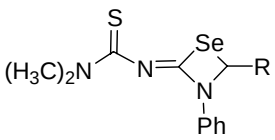


Figure 1. X-Ray Crystal Structure of *N*-(3,4-Diphenyl-1,3-selenazetidin -2-ylidene)-*N'*,*N'*-dimethylthiourea (**3a**) (ORTEP drawing, 30% thermal ellipsiods).

The reaction of **1** was studied with four imines (Table 1). The structure of **3a** was elucidated by IR, MS, ^{1}H-, ^{13}C-, ^{77}Se-NMR, COSY, HMQC and HMBC spectral data and X-ray analysis. The structures of products (**3b-d**) were determined by comparing the spectral data with those of **3a**. The X-ray crystal structure of *N*-(3,4-diphenyl-1,3-selenazetidin-2-ylidene)-*N'*,*N'*-dimethylthiourea (**3a**) was studied (Figure 1).[5] The bond angle of the selenium atom C(5)-Se(1)-C(7) in **3a** was 69.3(3)°, consistent with the previously reported value for 2,4-diimino-1,3-selenazetidine[3] and selenetane.[6] The selenazetidine ring is planar and imino group of **3a** are (*Z*)-configured. Furthermore, the arrangement of S2, C3, N4, C5, Se1, C7, N6 and C15 atoms is co-planar (dihedral angle: S(2)-C(3)-N(4)-C(5) -3.1(8), C(7)-Se(1)-C(5)-N(4) 176.6(7), C(7)-Se(1)-C(5)-N(6) -3.0(4), N(4)-C(5)-N(6)-C(15) -1.3(10), Se(1)-C(5)-N(6)-C(15) 178.4(5), N(4)-C(5)-N(6)-C(7) -175.6(6), Se(1)-C(5)-N(6)-C(7) 4.1(5), C(5)-N(6)-C(7)-Se(1) -3.8(4) and C(15)-N(6)-C(7)-Se(1) -178.5(5)°). The structure of the [4+2] cycloadduct product,

6-amino-2*H*-1,3,5-thiadiazine-4-selone (**4**), was ruled out by the X-Ray crystal analysis of the product. As a method of structural determination of compound (**3**), we found it useful to confirm significant difference of chemical shifts between selenazetidines[3] and selenoureas[1a,7-10] including cyclic selenoureas[8,11] in ^{77}Se NMR spectra. The signal in ^{77}Se NMR spectra of selenazetidines observed around δ 750, while chemical shifts of selenoureas appear in the range δ 170-340 in ^{77}Se NMR spectra. In the case of compound (**4**), the chemical shifts should be a range of chemical shifts of selenoureas. Chemical shifts of ^{77}Se NMR spectra for products (**3**) appeared at δ 756.9±2.24 which give evidence of the 1,3-selenazetidine structure (Table 2). We feel that these regularities, if found to be general, may be an important aid for determining structures of organoselenium compounds for which such NMR information is not available.



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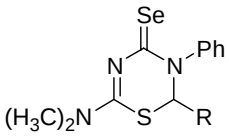

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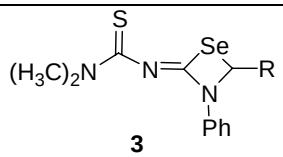
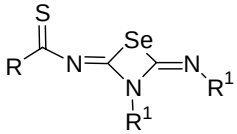
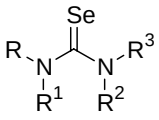
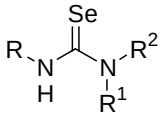
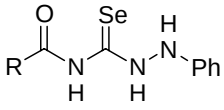
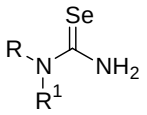
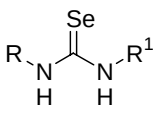
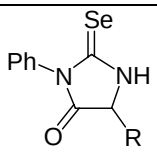
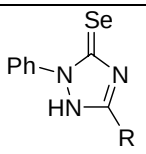
Table 2. Chemical shifts in ^{77}Se NMR of 1,3-selenazetidines and selenoureas.

	 **3**			
^{77}Se NMR (δ)	756.9±2.24	753.2±1.97[a]	336.3±20.3[b]	177.7±7.71[b]

					
^{77}Se NMR (δ)	298.3±8.19[c]	218.4±21.6[d]	189.2±32.5[e]	267.8±16.1[f]	88.6±1.07[c]

a: ref. 3a, *Heterocycles*, 2006, **68**, 1267. b: ref.7, *J. Org. Chem.*, 2002, **67**, 1008. c: ref. 8, *Heterocycles*, 2006, **68**, 1191. d: ref.9, *Tetrahedron Lett.*, 2001, **42**, 6333. e: ref. 1a and 10, *Chem. Lett.*, 2006, **35**, 626. *Synth. Commun.*, 2002, **32**, 3075. *J. Org. Chem.*, 1999, **64**, 6473. f: ref. 11, *J. Heterocycl. Chem.*, in press.

Previously, reactions of acyl isocyanates or thioacyl isocyanates with carbodiimides or benzylideneamines gave [4+2] cycloadducts, 2*H*-1,3,5-oxadiazin-4-ones or 2*H*-1,3,5-thiadiazin-4-ones,

respectively,[12] whilst the present reaction using isoselenocyanates afforded [2+2] cycloadducts, 1,3-selenazetidine (**3**).

Thus, selenium-nitrogen containing four-membered ring heterocycles have been prepared using thioacyl isoselenocyanates. The use of the thioacyl isoselenocyanates is one of the most efficient methods for the synthesis of heterocyclic compounds.

EXPERIMENTAL

General

The ^{77}Se chemical shifts were expressed in ppm deshielded with respect to Me_2Se. $^2J(^{77}Se\text{-}^1H)$ values are observed as ^{77}Se satellites of the ^{1}H NMR spectra.

Synthesis of *N*-(3,4-Diphenyl-1,3-selenazetidin-2-ylidene)-*N'*,*N'*-dimethylthiourea (3a)

Thiocarbamoyl chloride (0.25 g, 2.0 mmol) was added to THF solution (10 mL) of potassium selenocyanate (0.28 g, 2.0 mmol). The reaction mixture was stirred for 1 h under argon atmosphere. To the reaction mixture, *N*-benzylideneaniline (0.18 mL, 1.0 mmol) was added then refluxed for 5 hour. The mixture was extracted with diethyl ether and washed with water, and the organic layer was separated, dried over Na_2SO_4, and evaporated. The residue was subjected to flash column chromatography on silica gel using hexane : Et_2O (5 : 1) as the eluent, giving **3a** (0.12 g, 33%) as colorless crystals.

Mp: 184.1-185.3ºC, IR (KBr): 1591, 1610 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.43 (3H, s, CH_3-N), 3.45 (3H, s, CH_3-N), 6.41 (1H, s, CH, $^2J(^{77}Se\text{-}^1H)$ = 6.05 Hz), 7.01-7.06 (1H, m, Ar) 7.19-7.39 (7H, m, Ar), 7.52-7.57 (2H, m, Ar), ^{13}C NMR (125 MHz, $CDCl_3$): δ 39.5, 41.0, 68.9, 119.1, 123.8, 125.6, 127.9, 128.8, 129.1, 137.7, 140.0, 169.0, 189.2, ^{77}Se NMR (95 MHz, $CDCl_3$): δ 756.7, MS (CI): *m/z* = 376 [M^++1]. A crystal data of **3a**. $C_{17}H_{17}N_3S_{0.90}Se_{1.10}$, FW = 379.16, Crystal system Monoclinic, Space group $P2_1/c$, a = 17.4250(17) Å, b = 5.7575(6) Å, c = 17.3628(17) Å, β = 110.856(5)°, Z = 4, ρ_{calcd} = 1.547 g/cm^3, Limiting indices $-18 \leqq h \leqq 18$, $-6 \leqq k \leqq 6$, $-18 \leqq l \leqq 18$, Reflections collected 16908, Independent reflections 2119, Goodness-of-fit on F^2 1.090, Final R indices [$I>2\sigma(I)$] $R1$ = 0.0570, $wR2$ = 0.1265, R indices (all data) $R1$ = 0.0777, $wR2$ = 0.1380. Selected bond lengths [Å], angles [°] and torsion angles [°] for **3a**. Se(1)-C(5) 1.905(6), Se(1)-C(7) 2.054(6) S(2)-C(3) 1.753(7), N(2)-C(3) 1.328(8), C(3)-N(4) 1.377(8), N(4)-C(5) 1.285(8), C(5)-N(6) 1.366(8), N(6)-C(15) 1.427(8), N(6)-C(7) 1.472(8), C(7)-C(8) 1.482(9), C(5)-Se(1)-C(7) 69.3(3), N(6)-C(5)-Se(1) 97.4(4), C(5)-N(6)-C(7) 105.1(5), N(6)-C(7)-Se(1) 87.9(4)°, S(2)-C(3)-N(4)-C(5) -3.1(8), C(7)-Se(1)-C(5)-N(4) 176.6(7), C(7)-Se(1)-C(5)-N(6) -3.0(4), N(4)-C(5)-N(6)-C(15) -1.3(10), Se(1)-C(5)-N(6)-C(15) 178.4(5), N(4)-C(5)-N(6)-C(7) -175.6(6), Se(1)-C(5)-N(6)-C(7) 4.1(5), C(5)-N(6)-C(7)-Se(1) -3.8(4) and C(15)-N(6)-C(7)-Se(1) -178.5(5) for all data.[5]

***N*-(3-Phenyl-4-*p*-tolyl-1,3-selenazetidin-2-ylidene)-*N'*,*N'*-dimethylthiourea (3b)**

Mp: 162.5-163.8ºC, IR (KBr): 1590, 1608 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 2.30 (3H, s, CH_3), 3.42 (3H, s, CH_3-N), 3.45 (3H, s, CH_3-N), 6.39 (1H, s, CH, $^2J(^{77}Se\text{-}^1H)$ = 10.5 Hz), 7.01-7.05 (1H, m, Ar), 7.08-7.12 (2H, m, Ar), 7.23-7.29 (4H, m, Ar), 7.52-7.56 (2H, m, Ar), ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 39.4, 41.0, 68.7, 119.2, 123.8, 125.6, 128.8, 129.7, 134.6, 137.8, 140.0, 168.8, 189.2, ^{77}Se NMR (95 MHz, $CDCl_3$): δ 755.9, MS (CI): *m/z* = 390 [M^++1].

***N*-(4-*p*-Chlorophenyl-3-phenyl-1,3-selenazetidin-2-ylidene)-*N'*,*N'*-dimethylthiourea (3c)**

Mp: 172.3-173.0ºC, IR (KBr): 1590, 1604 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 3.43 (3H, s, CH_3-N), 3.45 (3H, s, CH_3-N), 6.37 (1H, s, CH, $^2J(^{77}Se\text{-}^1H)$ = 9.74 Hz), 7.03-7.08 (1H, m, Ar), 7.24-7.32 (6H, m, Ar), 7.48-7.54 (2H, m, Ar), ^{13}C NMR (125 MHz, $CDCl_3$): δ 39.5, 41.0, 68.5, 119.1, 124.0, 126.9, 128.9, 129.3, 133.4, 136.5, 139.8, 169.1, 189.2, ^{77}Se NMR (95 MHz, $CDCl_3$): δ 760.0, MS (CI): *m/z* = 410 [M^++1].

***N*-(4-*p*-Isopropylphenyl-3-phenyl-1,3-selenazetidin-2-ylidene)-*N'*,*N'*-dimethylthiourea (3d)**

Mp: 190.3-191.2ºC, IR (KBr): 1590, 1605 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$): δ 1.22 (6H, d, *J* = 6.87 Hz, CH_3), 2.82-2.90 (1H, m, CH), 3.43 (3H, s, CH_3-N), 3.45 (3H, s, CH_3-N), 6.40 (1H, s, CH), 7.01-7.06 (1H, m, Ar), 7.14-7.17 (2H, m, Ar), 7.24-7.32 (4H, m, Ar), 7.53-7.58 (2H, m, Ar), ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.8, 33.8, 39.4, 41.0, 68.7, 119.2, 123.7, 125.6, 127.1, 128.8, 134.9, 140.0, 148.7, 169.4, 189.2, ^{77}Se NMR (95 MHz, $CDCl_3$): δ 754.8, MS (CI): *m/z* = 418 [M^++1].

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5. Crystal structure data for **3a**: $C_{17}H_{17}N_3S_{0.90}Se_{1.10}$. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No. 612599 for **3a**. Copies of this information can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: + 44 1233 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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