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Synthesis of 5-amino-2-selenoxo-1,3-imidazole-4-carboselenoamides by the reaction of isoselenocyanates with aminoacetonitriles

Nobuhito Tanahashi [a], Mamoru Koketsu [b,*]

[a] Department of Chemistry, Faculty of Engineering, Gifu University, Gifu 501-1193, Japan
[b] Department of Materials Science and Technology, Faculty of Engineering, Gifu University, Gifu 501-1193, Japan

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ABSTRACT

Reaction of isoselenocyanates with aminoacetonitriles afforded 4-amino-2-selenoxo-1,3-imidazole-2-selenones, whereas reaction with aminopropionitriles led to selenoureas. We confirmed that it is easy to distinguish between selenoamides and selenoureas by comparison of their chemical shift differences in the ^{77}Se NMR spectra.

Isoselenocyanates have emerged as powerful tools for the synthesis of heterocycles, because they are easy to prepare, relatively nontoxic, and safe to handle and store.[1] Isoselenocyanates are used in the synthesis of versatile selenium-containing compounds such as 1,3-oxaselenepane,[2] 3-selena-1-dethiacephem via the corresponding selenourea,[3] 1,3-selenazole,[4] 3*H*-1,2,4-triazole-3-selone,[5] 1,3-selenazetidine,[6] and 1,3-selenazolidine derivatives.[7] Recently, selenium-containing compounds showed significant biological activities, such as anti-inflammatory, analgesic, and antimicrobial activities,[8] skin melanin biosynthesis inhibitor,[9] and antioxidant activity.[10] Therefore, to identify and biologically characterize additional related active species, new selenium-containing compounds are required. Herein, we describe the synthesis of novel selenium-containing compounds by the reaction of isoselenocyanates with aminoacetonitriles.

Alkyl and aryl isoselenocyanates **1** were prepared by reactions of N-substituted formamides with an excess of triphosgene, selenium and triethylamine.[11] Initially, reaction of *p*-tolylisoselenocyanate (**1a**) with 2-(phenylamino)acetonitrile (**2a**, 1 equiv) was performed in toluene at room temperature and the effects of various bases were compared. When triethylamine (Et_3N) or pyridine was used, the reaction gave 5-amino-3-phenyl-2-selenoxo-*N*,1-di(4-tolyl)-1,3-imidazole-4-carboselenoamide (**3a**). Further, in the presence of K_2CO_3, DIPEA, or LHMDS, each reaction gave either a complex mixture or no product. However, when pyridine was used, the reaction afforded **3a** in higher yield as compared to that obtained when Et_3N was used. Moreover, in the absence of base, no product was identified and only staring materials were recovered. Next, we evaluated the relative stoichiometry of the reagents. The reaction of **1a** (1 equiv) with **2a** (1 equiv) in the presence of pyridine at room temperature gave **3a** in 19% yield after 4 h. When the amount of **1a** was increased to 2 equiv (2:1 ratio, **1a**/**2a**), the yield of product **3a** was more than doubled (69%). It was subsequently confirmed that this reaction consumed 2 equiv of isoselenocyanate **1** for each equivalent of **2** to form product **3**. Finally, we compared the effects of solvents, such as ethanol, chloroform, dichloromethane, dimethylformamide, THF and toluene, for this reaction. The reaction using toluene exclusively formed **3a** in the highest yield. These results suggested the following optimized conditions: *p*-tolylisoselenocyanate (**1a**, 2 equiv) is reacted with 2-(phenylamino)acetonitrile (**2a**, 1 equiv) in the presence of pyridine at room temperature in toluene for 1 day yielding 5-amino-3-phenyl-2-selenoxo-*N*,1-di(4-tolyl)-1,3-imidazole-4-carboselenoamide (**3a**) in 69% yield (Table 1).

The structure of **3a** was elucidated by IR, NMR (^{1}H, ^{13}C, and ^{77}Se), 2D NMR (COSY, HMQC, and HMBC), MS, and elemental analysis. Under similar conditions, the reactions of five different alkyl and aryl isoselenocyanates **1** with 2-(phenylamino)acetonitrile (**2a**) or methylaminoacetonitrile (**2b**) gave the corresponding 5-amino-2-selenoxo-1,3-imidazole-4-carboselenoamides **3** in moderate to high yields (Table 1). The structures of products **3b**–**3j** were determined by comparing their spectral data with that of **3a**.

To confirm the structure of **3e**, we carried out an X-ray analysis of the crystallized compound.[12] The ORTEP drawing depicted in Figure 1 shows the molecular structure of **3e**. The four C–N bond

* Corresponding author. Tel.: +81 58 293 2619; fax: +81 58 293 2794.
E-mail address: koketsu@gifu-u.ac.jp (M. Koketsu).

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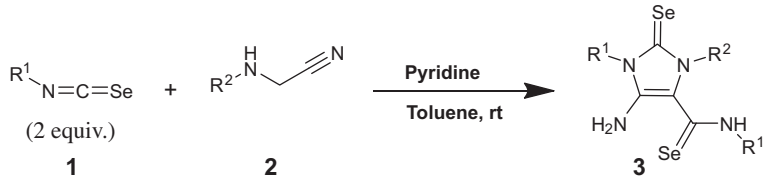
Table 1
Synthesis of 5-amino-2-selenoxo-1,3-imidazole-4-carboselenoamides (**3**) by the reactions of isoselenocyanates **1** with aminoacetonitriles **2**



Entry	R^1	R^2	Time	Yield (%)
1	4-$CH_3C_6H_4$**1a**	C_6H_5**2a**	1 day	69 (**3a**)
2	C_6H_5**1b**	C_6H_5**2a**	1 day	51 (**3b**)
3	4-ClC_6H_4**1c**	C_6H_5**2a**	1 day	93 (**3c**)
4[a]	2-$CH_3C_6H_4$**1d**	C_6H_5**2a**	1 day	28 (**3d**)
5	Benzyl **1e**	C_6H_5**2a**	1 day	78 (**3e**)
6	4-$CH_3C_6H_4$**1a**	CH_3**2b**	1 h	80 (**3f**)
7	C_6H_5**1b**	CH_3**2b**	1 h	56 (**3g**)
8	4-ClC_6H_4**1c**	CH_3**2b**	1 h	81 (**3h**)
9	2-$CH_3C_6H_4$**1d**	CH_3**2b**	1 h	72 (**3i**)
10	Benzyl **1e**	CH_3**2b**	1 h	73 (**3j**)

[a] Reflux.

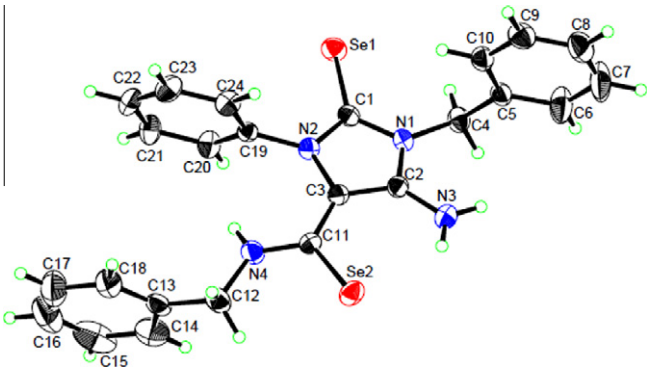


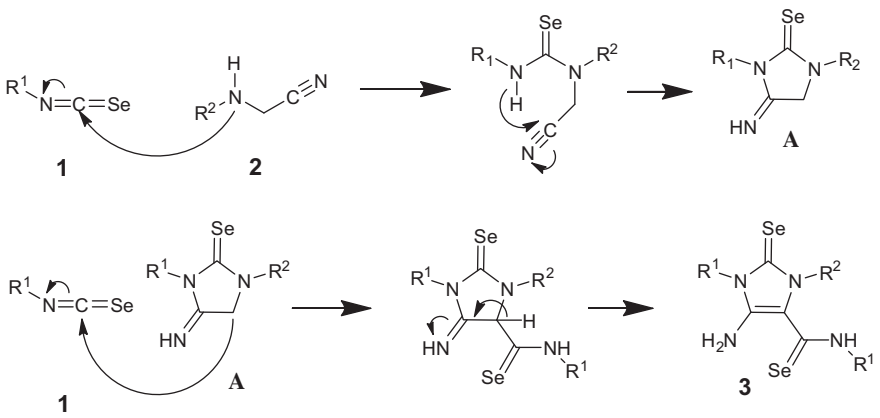
Figure 1. X-ray crystal structure of 5-amino-*N*,1-dibenzyl-3-phenyl-2-selenoxo-1,3-imidazole-4-carboselenoamide (**3e**) (ORTEP drawing).

lengths of C1–N2 (1.346(5) Å), C1–N1 (1.369(4) Å), N1–C2 (1.363(5) Å), and C2–N3 (1.436(4) Å) in the imidazole ring of **3e** are shorter than the typical single-bond length of 1.47 Å.[13] Atoms Se1, C1, N1, C2, C3, N2, C11, Se2, and N3 atoms are all coplanar.

The formation of **3** could be explained by the mechanism illustrated in Scheme 1. The reaction of **1** with **2** is initiated by the nucleophilic addition of the nitrogen atom of **2** to the electrophilic carbon atom of **1** affording the selenourea, which is subsequently cyclized to give 4-imino-1,3-imidazoline-2-selenone **A**. Next, the carbanion of 1,3-imidazolidine ring **A** attacks the electrophilic carbon of another molecule of **1** to form a carboselenoamide, which subsequently tautomerizes to the more stable amine **3**.

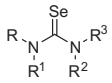
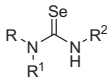
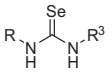
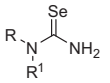
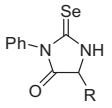
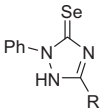
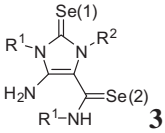
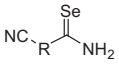
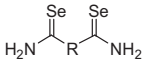
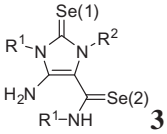
In the case of the reaction of an aminoacetonitrile **2** with an isothiocyanate or isocyanate in the absence of base, equimolar quantities of the isothiocyanate or isocyanate were consumed to yield a cyanomethylthiourea and 4-amino-1,3-imidazolidine-2-thione or a cyanomethylurea and 4-amino-1,3-imidazolidin-2-one, respectively.[14] The present reaction required pyridine and 2 equiv of isoselenocyanate **1** to obtain 2-selenoxo-1,3-imidazole-5-carboselenoamides **3**.

Recently, we have reported interesting spectral features of ^{77}Se NMR spectra and selenium coupling in ^{1}H NMR. The difference in the chemical shift between diacyl selenides (R–CO–Se–CO–R) and diacyl diselenides (R–CO–Se–Se–CO–R) can facilitate their detec-



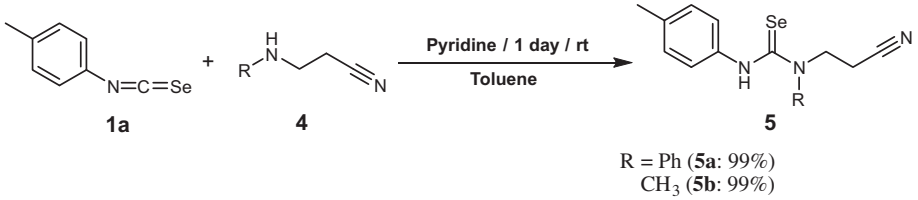
Scheme 1. Mechanism of reaction of isoselenocyanates with aminoacetonitriles.

Table 2
Chemical shifts of selenocarbonyl group in selenoureas and selenoamides

	Selenoureas						Se(1)	
	 **A**	 **B**	 **C**	 **D**	 **E**	 **F**	 **3**	
							R_2 = Ph	R_2 = CH_3
Se[a]	336.2 ± 20.3[c]	177.7 ± 7.7[c]	194.7 ± 53.0[d]	225.7 ± 13.3[e]	267.8 ± 16.1[f]	88.7 ± 1.1[g]	137.9 ± 24.3	94.5 ± 19.3
C=Se[b]	193.4 ± 3.1[c]	180.2 ± 0.6[c]	177.3 ± 1.6[d]	176.4 ± 1.7[e]	183.6 ± 0.8[f]	158.5 ± 1.4[g]	161.8 ± 0.3	158.6 ± 0.9
	Selenoamides						Se(2)	
	 **G**	 **H**	 **I**	 **J**			 **3**	
							R_2 = Ph	R_2 = CH_3
Se[a]	701.5 ± 41.7[h]	629.3 ± 53.7[i]	614.9 ± 83.7[k]	543.6 ± 62.7[k]			491.3 ± 72.6	544.3 ± 19.2
C=Se[b]	203.3 ± 1.8[h]	212.4 ± 6.7[j]	210.6 ± 4.4[k]	208.4 ± 3.7[k]			174.9 ± 0.7	179.4 ± 0.1

[a] Average chemical shift of selenium in ^{77}Se NMR spectra.
[b] Average chemical shift of selenocarbonyl carbon in ^{13}C NMR spectra.
[c] Ref. 17, *J. Org. Chem.*, **2002**, *67*, 1008–1011.
[d] Ref. 18, *Synth. Commun.*, **2002**, *32*, 3075–3079.
[e] Ref. 19, *Tetrahedron Lett.*, **2001**, *42*, 6333–6335.
[f] Ref. 20, *J. Heterocycl. Chem.*, **2007**, *44*, 79–81.
[g] Ref. 21, *Heterocycles*, **2006**, *68*, 1191–1200.
[h] Ref. 22, *Heteroat. Chem.*, **2002**, *13*, 195–198.
[i] Ref. 23, *Molecules*, **2009**, *14*, 884–892.
[j] Ref. 24, *Chem. Lett.*, **1998**, 1287–1288.
[k] Ref. 25, *Heteroat. Chem.*, **2003**, *14*, 106–110.

tion in the ^{77}Se NMR spectra. While the difference between the chemical shift of the carbonyl C-atoms of a diacyl selenide and that of a diacyl diselenide in ^{13}C NMR spectra is not significant, the corresponding difference in the chemical shift of selenium in ^{77}Se NMR spectra between the two species is substantial.[15] Additionally, selenium shows strong coupling with the *trans* proton with respect to selenium atom at an exocyclic double bond, whereas similar coupling with the *cis* proton is not observed.[3,16] Furthermore, structural confirmation studies can take advantage of the significant differences in the chemical shift between selenazetidines and selenoureas, including cyclic selenoureas, in ^{77}Se NMR spectra.[6a] Thus, ^{77}Se NMR spectra give important information for structural analysis and confirmation. In this study, we isolated 2-selenoxo-1,3-imidazole-4-carboselenoamides **3**, incorporate a cyclic selenourea and a selenoamide group in the structure. Reported chemical shifts of selenocarbonyl groups in selenoureas and selenoamides are summarized in Table 2. In ^{13}C NMR spectra, most chemical shifts for carbonyl carbons of selenocarbonyl groups in selenoureas are observed at higher fields than those of selenoamides; however, the difference is minimal. In contrast, the chemical shift of the C-atom of the selenocarbonyl group in selenoureas **A** (193.4 ± 3.1 ppm), **B** (180.2 ± 0.6 ppm), **C** (177.3 ± 1.6 ppm), and **E** (183.6 ± 0.8 ppm) is observed at lower fields than the chemical shift (174.9 ± 0.7 ppm or 179.4 ± 0.1 ppm) of Se2 of the selenoamide group in compound **3**. Similar to the above-reported finding comparing diacyl selenides and diacyl diselenides, the difference in the chemical shift of Se between selenoureas and selenoamides in the ^{77}Se NMR spectra is greater than that of C in the corresponding ^{13}C NMR spectra, and therefore, the two species can be distinguished easily. Values for the chemical shift of Se in selenoureas and selenoamides do not reverse in the ^{77}Se NMR spectra. In the case of selenoureas including compounds **3**, signals for Se-atoms are observed in the range of 88–336 ppm. The chemical shift values for selenium in selenoamides fall in the range of 491–702 ppm, which is obviously lower than those for selenoureas. The average chemical shift (94.5 ± 19.3 ppm) of Se1 (urea) for compound **3** (R^2 = methyl) is at a higher field than that of 3 (R^2 = phenyl, 137.9 ± 24.3 ppm). The average chemical shift (544.3 ± 19.2 ppm) of Se2 (amide) for compound **3** (R^2 = methyl) is also at lower field than that of 3 (R^2 = phenyl, 491.3 ± 72.6 ppm). This clearly reflects the variable pattern of electron density provided by the alkyl and aryl substituents around the selenium atom in **3**. Furthermore,



1a **4** **5**

R = Ph (**5a**: 99%)
CH_3 (**5b**: 99%)

Scheme 2. Reaction of *p*-tolylisoselenocyanate (**1a**) with 3-aminopropionitrile (**4**).

we can distinguish between the selenoamide and selenourea fragments by their significant differences in their chemical shifts in the ^{77}Se NMR spectra.

Next, we evaluated the reaction of *p*-tolylisoselenocyanate (**1a**) with a homolog of **2**, 3-aminopropionitrile (**4**) using the same reaction conditions. We expected the generation of a six-membered pyrimidine derivative. However, reactions of **1a** with two examples of **4** afforded the corresponding acyclic selenourea derivatives **5** in quantitative yields (Scheme 2).

We have demonstrated the one-pot synthesis of 5-amino-2-selenoxo-1,3-imidazole-4-carboselenoamides **3** generated by reacting isoselenocyanates **1** with 2-aminoacetonitriles **2**. The reaction of **1** with 3-aminopropionitrile **4** gave the corresponding selenoureas **5** in quantitative yield. In conclusion, we confirmed that it is easy to distinguish between selenoamides and selenoureas by comparison of their chemical shift differences in the ^{77}Se NMR spectra.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.119.

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