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Direct synthesis of novel 2-imino-1,3-selenazolidine derivatives from *O*-methanesulfonyl β-amino alcohol hydrochlorides

Shigeo Ueda,[a,*] Hideo Terauchi,[a,b] Kenji Suzuki[a] and Nobuhide Watanabe[a]

[a]*Chemistry Research Laboratories, Dainippon Pharmaceutical Co., Ltd, Enoki-cho 33-94, Suita, Osaka 564-0053, Japan*
[b]*Pharmaceutical Research and Technology Center, Dainippon Pharmaceutical Co., Ltd, Ebie 1-5-51, Fukushima, Osaka 553-0001, Japan*

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Abstract—Recently, we have reported that 4,5-dialkylsubstituted 2-imino-1,3-azolidine derivatives (**1**) strongly inhibit inducible nitric oxide synthase (iNOS). To our knowledge, only few methods have been reported for the synthesis of 4,5-dialkylsubstituted 2-imino-1,3-selenazolidine derivatives (**2**), which are the selenium analogue of **1**. Herein, we report the direct synthesis of **2** from the corresponding *O*-methanesulfonyl β-amino alcohol hydrochlorides using potassium selenocyanate and evaluation for the inhibitory activity against iNOS of the newly synthesized selenazolidine derivatives.

Selenium-containing compounds have enthusiastically been studied in the fields of chemistry and pharmacology, because they biologically act as antioxidants and can inhibit human fibro sarcoma DNA fragmentation, eukaryotic elongation factor-2 kinase and inducible nitric oxide production.[1,2] In addition, selenium itself has pharmacologically been explored for the prevention of prostate and ovarian cancer.[3] Therefore, the biological role of compounds containing selenium is subject to intense current interest.

We have recently reported that 4,5-dialkyl-2-imino-1,3-azolidine derivatives (**1**, Chart 1)[4] show strong inhibitory activity against inducible nitric oxide synthase (iNOS). Combining this finding with the results of previous studies,[1–3] we anticipated that the selenium analogues of **1** that are 4,5-dialkylsubstituted 2-imino-1,3-selenazolidine derivatives (**2**) would pharmacologically be active and might display a similar profile to that of **1** (Chart 1). However, to our knowledge, no synthetic method of **2** has been reported.

(±) -*cis*-**1a**: (X = S, $R^1 = R^2$ = Et)
(±) -*trans*-**1b**: (X = S, $R^1 = R^2$ = Et)

Chart 1.

According to a recent report by Xu,[5] when *O*-methanesulfonyl β-amino alcohol hydrochlorides are reacted with sodium sulfite under appropriate reaction conditions, aziridines are produced as intermediates. Subsequent attack of sodium sulfite as a nucleophile on the aziridine ring affords taurine derivatives. On the basis of this reported mechanism, we hypothesized that reaction of *O*-methanesulfonyl β-amino alcohol hydrochlorides with potassium selenocyanate (KSeCN) instead of sodium sulfite would lead to **2**. Herein, we first report the direct synthesis of novel 4,5-dialkylsubstituted 2-imino-1,3-selenazolidine derivatives from the corresponding *O*-methanesulfonyl β-amino alcohol hydrochlorides using potassium selenocyanate, and evaluate the inhibitory activity against iNOS of the newly synthesized compounds.

Initially, we targeted the synthesis of the 4,5-diethylsubstituted derivative (±)-*cis*-**9a** as representative of **2** because its thiazolidine analogue [(±)-*cis*-**1a**, Chart 1] shows strong inhibitory activity against iNOS.[4b]

Keywords: 1,3-Selenazolidine; Aziridine; iNOS.
* Corresponding author. Tel.: +81 6 6337 5901; fax: +81 6 6338 7656; e-mail: shigeo-ueda@dainippon-pharm.co.jp

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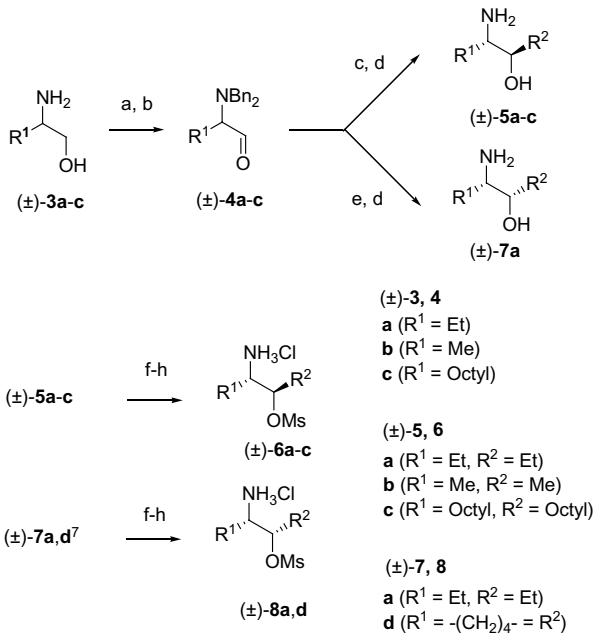
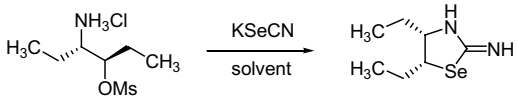


Scheme 1. Synthesis of *O*-methanesulfonyl β-amino alcohol hydrochlorides (±)-**6a**–**c** and (±)-**8a**,**d**. Reagents and conditions: (a) BnBr, K_2CO_3, CH_3CN, 60 °C; (b) Swern oxidn; (c) R^2MgBr, THF, 0 °C; (d) H_2, 20% $Pd(OH)_2$–C, MeOH; (e) $(R^2)_2Zn$, toluene, 0 °C; (f) Boc_2O, CH_2Cl_2; (g) MsCl, Et_3N, CH_2Cl_2; (h) 30% HCl/EtOH.

As shown in Scheme 1, the requisite *O*-methanesulfonyl β-amino alcohol hydrochloride (±)-**6a** was prepared from the corresponding amino alcohol (±)-**3a** in seven steps according to a previously reported procedure.[4b,5,6]

Reaction conditions for the conversion of (±)-**6a** to (±)-*cis*-**9a** were optimized as shown in Table 1. Reaction of (±)-**6a** with 2 equiv of KSeCN in H_2O at 80 °C gave the best yield of (±)-*cis*-**9a**[8] (89%, entry 2), however, this reaction hardly proceeded when using the same equivalent of KSeCN at low temperature or 1 equiv of KSeCN even at high temperature (Table 1, entries 1 and 3). The production of (±)-*cis*-**9a** from (±)-**6a** was also attempted in other solvents, that is MeOH, EtOH, DMF and THF.

Table 1. Optimization of reaction for the conversion of (±)-**6a** using KSeCN to 2-imino-1,3-selenazolidine (±)-*cis*-**9a**[a]



(±)-**6a** (±)-*cis*-**9a**

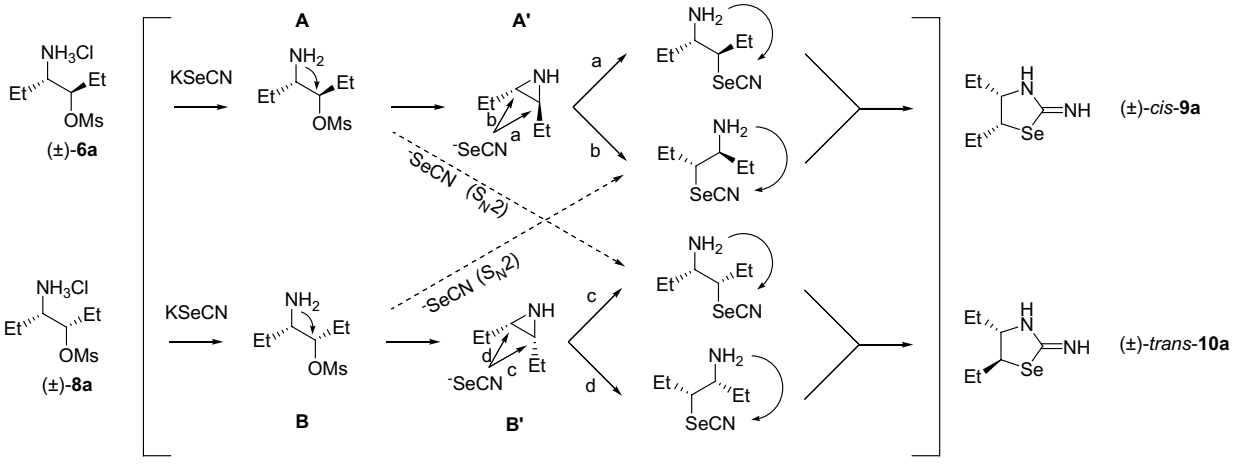
Entry	KSeCN (equiv)	Solvent	Time (h)	Temp (°C)	Yield (%)
1	2	H_2O	48	0	—[b]
2	2	H_2O	1	80	89
3	1	H_2O	24	80	<5
4	2	MeOH	1	Reflux	60
5	2	EtOH	1	Reflux	75
6	2	DMF	1	100	71
7	2	THF	1	Reflux	71

[a] Isolated as a fumarate.
[b] Not yielded.

Interestingly, all solvents led to moderate to good yield of (±)-*cis*-**9a** (Table 1, entries 4–7).

The possible mechanism for the conversion of (±)-**6a** to (±)-*cis*-**9a** is shown in Scheme 2 and may be explained as follows. Initially, KSeCN neutralizes (±)-**6a** to afford the free methanesulfonate **A**. The intermediate **A** undergoes cyclization to form the aziridine **A′**, which is subsequently attacked by the selenocyanic ion ($^-$SeCN) to open the aziridine ring. Finally intramolecular cyclization furnishes (±)-*cis*-**9a**. When $^-$SeCN attacks the carbon atom connected to the mesylate (–OMs) of intermediate **A** before aziridination (Scheme 2, dotted arrow down), the configuration of the mesylate carbon is inverted, followed by intramolecular cyclization, to afford (±)-*trans*-**10a**.

On the other hand, when (±)-**8a** is reacted with KSeCN under reaction conditions similar to that under which (±)-*cis*-**9a** was produced from (±)-**6a**, (±)-*trans*-**10a** is produced via intermediate **B** and **B′**. When $^-$SeCN attacks the carbon atom connected to the mesylate



Scheme 2. Possible mechanism for the synthesis of 2-imino-1,3-selenazolidine derivatives (±)-*cis*-**9a** and (±)-*trans*-**10a**.

(–OMs) before aziridination (Scheme 2, dotted arrow up), the configuration of the mesylate carbon is inverted, followed by intramolecular cyclization, to afford (±)-*cis*-**9a**.

In order to confirm the mechanism explained above, we synthesized the optically active isomer of *cis*-**9a** from the corresponding optically active amino alcohol (*S*)-**3a** according to a method similar to that for the synthesis of (±)-*cis*-**9a** from (±)-**6a**, and examined its stereochemistry using X-ray analysis. Based on the mechanism, the synthesized compound should have a (4*S*,5*R*) configuration. The ORTEP view revealed that the synthesized compound had a *cisoid* configuration (Fig. 1). In addition, the analysis of Flack parameter[9] together with experimental data on this compound confirmed the absolute configuration of the synthesized compound as (4*S*,5*R*).

Having confirmed the mechanism for the conversion of (±)-**6a** to (±)-*cis*-**9a** and optimized the reaction conditions, we next examined the conversion of various *O*-methanesulfonyl β-amino alcohol hydrochlorides [(±)-**6b**,**c** and (±)-**8a**,**d**] into 2-imino-1,3-selenazolidines. The requisite hydrochlorides were synthesized by a method similar to that for the synthesis of (±)-**6a** (Scheme 1). As shown in Table 2, the hydrochlorides were transformed into the corresponding 1,3-selenazolidines (±)-*cis*-**9b**,**c** and (±)-*trans*-**10a**,**d** in moderate to satisfactory yield. In addition, potassium thiocyanate (KSCN) instead of KSeCN was reacted with (±)-**6a** under the same condition to afford (±)-*cis*-**1a** in good yield.

Finally, we evaluated the inhibitory activity against iNOS of two selected compounds, that is, (±)-*cis*-**9a**, (±)-*trans*-**10a** and their sulfur analogues according to a previously reported procedure.[4b] As shown in Table 3, the inhibitory activity of the selenazolidine derivatives against iNOS was very strong and in the same range as that of thiazolidine analogues. Therefore, selenazolidine derivatives may be expected to have pharmacological activity similar to that of thiazolidine derivatives.

As many aziridine or aziridinium ion derivatives have been reported as important intermediates for the synthesis of biologically active compounds,[10] our study add on to that concept by providing a direct synthetic method for the pharmacologically active 4,5-dialkylsubstituted 2-imino-1,3-selenazolidine derivatives via aziridine intermediates.

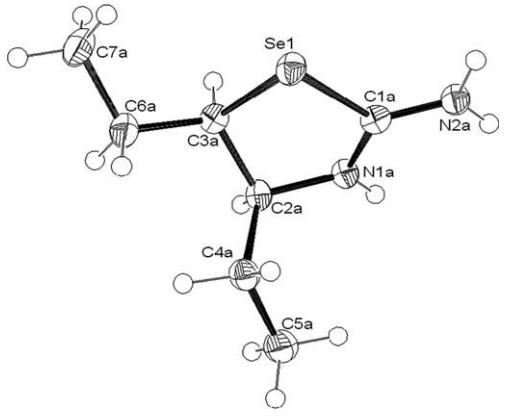
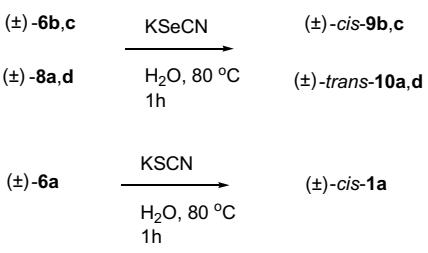
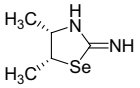
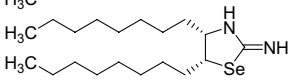
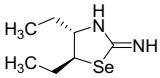
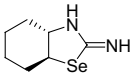
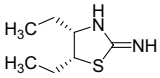


Figure 1. ORTEP view of X-ray structure of (4*S*,5*R*)-**9a**.

Table 2. Synthesis of 4,5-dialkyl-2-imino-1,3-selenazolidines (±)-*cis*-**9b**,**c**, (±)-*trans*-**10a**,**d** and 2-iminothiazolidine (±)-*cis*-**1a**[a]



Entry	Compound	Structure	Yield (%)
1	(±)-*cis*-**9b**		70
2	(±)-*cis*-**9c**		65
3	(±)-*trans*-**10a**		84
4	(±)-*trans*-**10d**		77
5	(±)-*cis*-**1a**		87

[a] Isolated as a fumarate except for (±)-*trans*-**10d**.

Table 3. Inhibitory activity of 4,5-diethylsubstituted 2-imino-1,3-selena and thiazolidine against iNOS[a]

Compound	Inhibitory activity IC_{50} (nM)[b]
(±)-*cis*-**9a**	96
(±)-*cis*-**1a**	34
(±)-*trans*-**10a**	18
(±)-*trans*-**1b**	14

[a] All compounds were evaluated as a fumarate.
[b] IC_{50} value for iNOS was determined by testing each compound at eight concentration according to previous report.[4b]

In conclusion, by reacting *O*-methanesulfonyl β-amino alcohol hydrochlorides with KSeCN, we provide here a direct synthetic method of the pharmacologically active 4,5-dialkylsubstituted 2-imino-1,3-selenazolidine derivatives via aziridine intermediates. This synthetic method will be helpful in the preparation of selenium-containing organic compounds. Further study is now in progress.

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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.2004.11.064.

References and notes

1. (a) Koketsu, M.; Fukuta, Y.; Ishihara, H. *Tetrahedron Lett.* **2001**, *42*, 6333–6335; (b) Tsuchii, K.; Ogawa, A. *Tetrahedron Lett.* **2003**, *44*, 8777–8780; (c) Tsuchii, K.; Doi, M.; Hirao, T.; Ogawa, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3490–3493; (d) Sasaki, M.; Hatta, M.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2004**, *45*, 1911–1913; (e) Silva, V. D.; Woznichak, M. M.; Burns, K. L.; Grant, K. B.; May, S. W. *J. Am. Chem. Soc.* **2004**, *126*, 2409–2413.
2. (a) Koketsu, M.; Ishihara, H.; Wu, W.; Murakami, K.; Saiki, I. *Eur. J. Pharm. Sci.* **1999**, *9*, 157–161; (b) Cho, S. I.; Koketsu, M.; Ishihara, H.; Matsushita, M.; Nairn, A. C.; Fukazawa, H.; Uehara, Y. *Biochim. Biophys. Acta* **2000**, *1475*, 207–215; (c) Park, Y. J.; Koketsu, M.; Kim, J. M.; Yeo, J. H.; Ishihara, H.; Lee, K. G.; Kim, S. Y.; Kim, C. K. *Biol. Pharm. Bull.* **2003**, *26*, 1657–1660.
3. (a) Taylor, P. R.; Parnes, H. L.; Lippman, S. M. *J. Natl. Cancer Inst.* **2004**, *96*, 645–647; (b) Sieja, K.; Talerczyk, M. *Gynecol. Oncol.* **2004**, *93*, 320–327; (c) Ghosh, J. *Biochem. Biophys. Res. Commun.* **2004**, *315*, 624–635.
4. (a) Ueda, S.; Terauchi, H.; Yano, A.; Ido, M.; Matsumoto, M.; Kawasaki, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 313–316; (b) Ueda, S.; Terauchi, H.; Yano, A.; Matsumoto, M.; Kubo, T.; Kyoya, Y.; Suzuki, K.; Ido, M.; Kawasaki, M. *Bioorg. Med. Chem.* **2004**, *12*, 4101–4116.
5. Xu, J. *Tetrahedron: Asymmetry* **2002**, *13*, 1129–1134.
6. (a) Higashiura, H.; Morino, H.; Matsuura, H.; Toyomaki, Y.; Ienaga, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1479–1481; (b) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed.* **1987**, *26*, 1141–1143; (c) Andrés, J. M.; Barrio, R.; Martínez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *J. Org. Chem.* **1996**, *61*, 4210–4213.
7. (±)-**7d** is commercially available.
8. Representative synthetic methods and characteristic data are given for (±)-*cis*-4,5-diethyl-2-iminoselenazolidine (**9a**): to a stirred solution of (±)-**6a**[4b] (1.88 g, 8.11 mmol) in water (17 mL) was added KSeCN (2.34 g, 16.2 mmol) at 0 °C and the reaction mixture was allowed to warm up to 80 °C with stirring for additional 2 h. The reaction mixture was then cooled in an ice bath, basified with 10% sodium hydroxy solution (17 mL), extracted with chloroform (20 mL × 2), dried with sodium sulfate and finally concentrated under reduced pressure, to give a crude brown oil. Purification of this crude oil by column chromatography using Chromatorex® (NH) gave (±)-*cis*-**9a** (1.49 g, 89%) as a yellow oil: ^{1}H NMR ($CDCl_3$): δ 0.96 (3H, t, J = 7.2 Hz), 1.05 (3H, t, J = 7.4 Hz), 1.48–1.67 (2H, m), 1.78–1.93 (2H, m), 3.84 (1H, dt, J = 8.4, 6.0 Hz), 3.97 (1H, ddd, J = 11.5, 5.5, 3.7 Hz), 4.74 (2H, br). APCI-MS *m*/*z* 206 $[M+H]^+$. This compound was treated with fumaric acid in EtOH/*n*-hexane solution to give its fumarate as a white solid, mp 138–142 °C. Anal. Calcd for $C_7H_{14}N_2Se{\cdot}C_4H_4O_4$: C, 41.13; H, 5.65; N, 8.72. Found: C, 41.15; H, 5.71; N, 8.71. Caution! KSeCN or HSeCN produced in situ is very stenchful.
9. Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; *X-ray crystallographic analysis*: a colourless prismatic crystal of this compound having approximate dimension of 0.7 × 0.5 × 0.3 mm were obtained from EtOH solution by slow evaporation at room temperature. All measurements were made on a Bruker APEX CCD detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods and refined by full-matrix least-squares methods with anisotropic temperature factors for non-H atoms. All hydrogen atoms calculated at idealized positions were included in the calculation of the structure factors. The crystal data are as follows: $C_9H_{16}O_2N_2Se$; M_r = 263.2; monoclinic; $P2_1$; a = 7.5976(8) Å; b = 17.1935(19) Å; c = 8.9684(10) Å; β = 102.713(2)°; V = 1142.8(2) Å^3; Z = 4; D_c = 1.530 g/cm^3; $F(000)$ = 536; μ(Mo Kα) = 32.65 cm^{-1}; T = 100(2) K; R = 0.023; S = 1.036. Flack's χ parameter (−0.011(7)) indicated that the absolute structure of this compound was 4*S* and 5*R* configuration. Full information on the crystal structure of this compound can be ordered from Cambridge Crystallographic Data Centre (CCDC); deposition number CCDC 249085.
10. (a) Morie, T.; Kato, S.; Harada, H.; Fujiwara, I.; Watanabe, K.; Matsumoto, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2565–2569; (b) Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5657–5664; (c) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599–619.