doi:10.1246/cl.2011.449
Published on the web April 9, 2011

Reaction of 2-(Aminomethyl)pyridine with Selenium Dioxide: Synthesis and Structure of Selenium-bridged Imidazo[1,5-*a*]pyridine Derivatives

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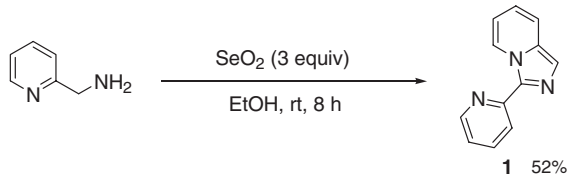
(Received February 7, 2011; CL-110105; E-mail: niyomura@isc.chubu.ac.jp)

Reaction of 2-(aminomethyl)pyridine with selenium dioxide leads to the formation of imidazo[1,5-*a*]pyridine (2-azaindolizine) skeleton in a single step. The major products of the reactions are 3-(2-pyridyl)imidazo[1,5-*a*]pyridine, bis[3-(2-pyridyl)imidazo[1,5-*a*]pyridin-1-yl] selenide, or the corresponding diselenide depending upon the reaction conditions. The structures of these selenium-bridged imidazo[1,5-*a*]pyridine derivatives are disclosed by X-ray crystal structural analyses. For the diselenide, the unusual dihedral angle C–Se–Se–C of 56.0° was observed indicating π–π intramolecular interaction between the fused six-membered rings.

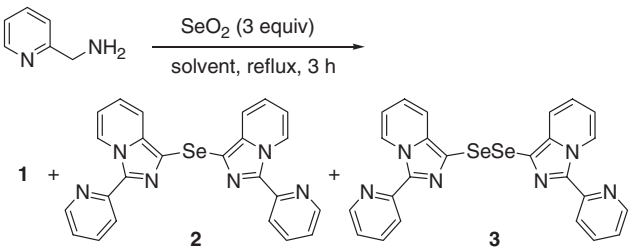
Imidazo[1,5-*a*]pyridine (2-azaindolizine) derivatives are important families of fused heteroaromatic compounds for pharmaceutical and material sciences due to their unique biological activity and fluorescence properties. Bioactive compounds having imidazo[1,5-*a*]pyridine skeletons have been extensively investigated, for example, as HIV-protease inhibitors,[1] 5-HT4 antagonists,[2] and MEK kinase inhibitors.[3] The imidazo[1,5-*a*]pyridine skeletons also have potential for application in display devices such as organic light-emitting diodes (OLED)[4] and thin-layer field effect diodes (FET).[5] Moreover, they have been studied as potential precursors of carbene ligands to transition metals.[6] Because of these backgrounds, a range of methods for syntheses of imidazo[1,5-*a*]pyridine derivatives have very recently been reported.[7]

In the course of our research on the facile synthesis of heterocycles using oxidation of active methylene compounds, we reported the reaction of 2-(aminomethyl)pyridine with cobalt chloride giving tetrapyridylpyrazine.[8] Further we recently reported on the one-pot synthesis of indolizine derivatives by the reaction of 2-(cyanomethyl)pyridine with selenium dioxide.[9] In this letter, we report the reaction of 2-(aminomethyl)pyridine and selenium dioxide to form new compounds bearing two imidazo[1,5-*a*]pyridine groups bridged by one or two selenium atoms. The reactions were affected greatly by reaction temperature and solvent.

Initially, we attempted the reaction of 2-(aminomethyl)pyridine with excess selenium dioxide (3 equiv) in ethanol at room temperature. The reaction for 8 h gave 3-(2-pyridyl)imidazo[1,5-*a*]pyridine (**1**)[10] in 52% yield (Scheme 1). Next, the same reaction was carried out in refluxing ethanol. The reaction proceeded smoothly for 3 h followed by removal of insoluble material and recrystallization to give bis[3-(2-pyridyl)imidazo-[1,5-*a*]pyridin-1-yl] selenide (**2**) in 51% yield with a small



Scheme 1.



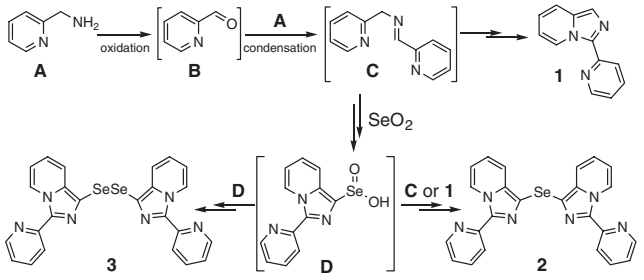
solvent	1	2	3
EtOH	small amount	51%	n.d.
H_2O	n.d.	25%	36%

n.d. : not detected

Scheme 2.

amount of **1** (Scheme 2).[11,12] The selenium-bridged imidazo[1,5-*a*]pyridine compound **2** was obtained as yellow crystals purified by recrystallization from hot ethanol. On the other hand, for the reaction in water as a solvent under reflux conditions, the compound with two 2-azaindolizyl groups bridged by two selenium atoms, bis[3-(2-pyridyl)imidazo[1,5-*a*]pyridin-1-yl] diselenide (**3**),[13] was obtained mainly in 36% yield together with monoselenide **2** (25% yield). In this case, the formation of **1** was not observed. A mixture of **2** and **3** was separated by column chromatography on silica gel using chloroform as eluent to give pure diselenide **3** as red to orange crystals.

Although the details of the reaction pathways are not clear, a plausible pathway for the reactions of 2-(aminomethyl)pyridine with selenium dioxide is shown in Scheme 3.[14] Initially, imine **C** may be formed from two molecules of 2-(aminomethyl)pyridine under oxidative conditions.[15] The imine **C** is cyclized intramolecularly and aromatized to give imidazo[1,5-*a*]pyridine **1**. The imine **C** reacts with selenium dioxide to afford the seleninic acid **D**. The seleninic acid **D** reacts with imine **C** to give monoselenide **2**. In the case of the reaction in water, mainly diselenide **3** is formed by the reaction of two molecules of **D**.[16]



Scheme 3.

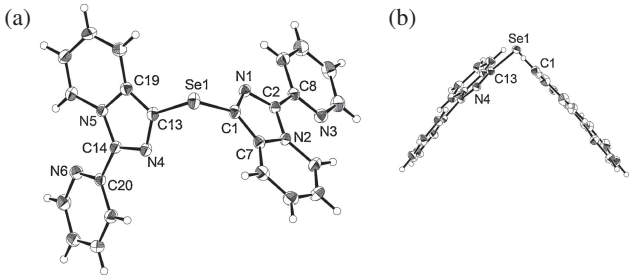


Figure 1. (a) ORTEP drawing of **2**. (b) Side view.

For the reactions of a separately prepared imine **C**[17] with selenium dioxide in refluxing ethanol, the formations of **1** and **2** are observed (9% and 8% isolated yields, respectively). In the case of the reaction in refluxing water, the formations of **2** (13%) and **3** (17%) are confirmed. The reactions of isolated **1** with selenium dioxide in ethanol or water under reflux resulted in the formation of neither monoselenide **2** nor diselenide **3**,[18] indicating that these selenides do not form through direct selenation of imidazo[1,5-*a*]pyridine by selenium dioxide. Furthermore, no exchange between **2** and **3** under the reaction conditions was observed.[19] These results indicate that the formations of **1**, **2**, and **3** are competitive process and are not in contradiction with the reaction pathway shown in Scheme 3.

The structures of new compounds, monoselenide **2** and diselenide **3** were determined by X-ray crystallography.[20] The ORTEP drawings of **2** and **3** are shown in Figures 1 and 2, respectively. For monoselenide **2**, the C–Se–C angle is 98.98(6)° and two imidazo[1,5-*a*]pyridine planes are perpendicular to each other forming roof-like structure (Figure 1b). Imidazo[1,5-*a*]-pyridine planes and pyridine rings are slightly twisted [N2–C2–C8–N3: 6.2(2)° and N5–C14–C20–N6: 15.1(2)°]. Diselenide **3** has a characteristic structure with an extremely narrow C–Se–Se–C torsion angle [C1–Se1–Se2–C13: −56.0(2)°].[21] Two six-membered rings of imidazo[1,5-*a*]pyridines show a significant overlap (Figures 2b and 2c). The distances between these planes are in the range of 3.207 to 3.952 Å, indicating intramolecular π–π interaction between these imidazo[1,5-*a*]pyridine rings. This conformation around the Se–Se bond might be stabilized by this π–π stacking interaction.[22] Imidazo[1,5-*a*]pyridine planes and pyridine rings are slightly twisted similarly to monoselenide **2** [N2–C2–C8–N3: −4.6(6)° and N5–C14–C20–N6: −11.8(5)°]. For the crystal packing of these imidazo[1,5-*a*]pyridine derivatives **2** and **3**, there is intermolecular π–π stacking interaction between the imidazo[1,5-*a*]pyridine rings (see Supporting Information).[12]

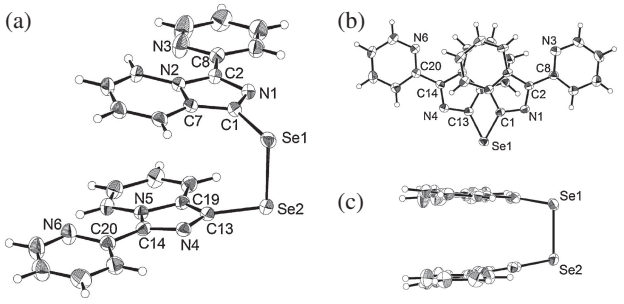


Figure 2. (a) ORTEP drawing of **3**. Two chloroform molecules (crystalline solvent) are omitted for clarity. (b) Top view. (c) Side view.

In summary, we found the reaction of 2-(aminomethyl)pyridine and selenium dioxide to give three types of imidazo[1,5-*a*]pyridine derivatives depending on the reaction temperatures and the solvents used. The reaction at room temperature in ethanol led to 3-(2-pyridyl)imidazo[1,5-*a*]pyridine with high selectively, whereas the reaction in ethanol or water under reflux conditions gave the products bearing two imidazo[1,5-*a*]pyridyl groups bridged by one or two selenium atoms. The structures of selenium-containing derivatives were determined by X-ray analyses, and the results have implied, in diselenide **3**, the intramolecular π–π interaction is present between two imidazo-[1,5-*a*]pyridyl groups. Further application of the present protocol providing imidazo[1,5-*a*]pyridines and those obtained is due in course.

O. N. thanks to the Kitasato University Research Grant for Young Researchers for financial support.

References and Notes

1 D. Kim, L. Wang, J. J. Hale, C. L. Lynch, R. J. Budhu, M. MacCoss, S. G. Mills, L. Malkowitz, S. L. Gould, J. A. DeMartino, M. S. Springer, D. Hazuda, M. Miller, J. Kessler, R. C. Hrin, G. Carver, A. Carella, K. Henry, J. Lineberger, W. A. Schleif, E. A. Emini, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129.

2 D. P. Becker, D. L. Flynn, A. E. Moormann, R. Nosal, C. I. Villamil, R. Loeffler, G. W. Gullikson, C. Moummi, D.-C. Yang, *J. Med. Chem.* **2006**, *49*, 1125.

3 S. Price, R. Heald, P. P. A. Savy, WO2009085980, **2009**.

4 a) M. Nakatsuka, T. Shimamura, Jpn. Kokai Tokkyo Koho JP 2001035664; M. Nakatsuka, T. Shimamura, *Chem. Abstr.* **2001**, *134*, 170632. b) G. Tominaga, R. Kohama, A. Takano, Jpn. Kokai Tokkyo Koho JP 2001006877; G. Tominaga, R. Kohama, A. Takano, *Chem. Abstr.* **2001**, *134*, 93136. c) D. Kitazawa, G. Tominaga, A. Takano, Jpn. Kokai Tokkyo Koho JP 2001057292; D. Kitazawa, G. Tominaga, A. Takano, *Chem. Abstr.* **2001**, *134*, 200276.

5 H. Nakamura, H. Yamamoto, PCT Int. Appl. WO 2005043630; H. Nakamura, H. Yamamoto, *Chem. Abstr.* **2005**, *142*, 440277.

6 a) M. Alcarazo, S. J. Roseblade, A. R. Cowley, R. Fernández, J. M. Brown, J. M. Lassaletta, *J. Am. Chem. Soc.* **2005**, *127*, 3290. b) S. J. Roseblade, A. Ros, D. Monge, M. Alcarazo, E. Álvarez, J. M. Lassaletta, R. Fernández, *Organometallics* **2007**, *26*, 2570. c) A. Fürstner, M.

Alcarazo, H. Krause, C. W. Lehmann, *J. Am. Chem. Soc.* **2007**, *129*, 12676. d) M. Nonnenmacher, D. Kunz, F. Rominger, T. Oeser, *J. Organomet. Chem.* **2007**, *692*, 2554.

7 a) F. Shibahara, A. Kitagawa, E. Yamaguchi, T. Murai, *Org. Lett.* **2006**, *8*, 5621. b) S. A. Siddiqui, T. M. Potewar, R. J. Lahoti, K. V. Srinvivasan, *Synthesis* **2006**, 2849. c) A. Moulin, S. Garcia, J. Martinez, J.-A. Fehrentz, *Synthesis* **2007**, 2667. d) F. Shibahara, R. Sugiura, E. Yamaguchi, A. Kitagawa, T. Murai, *J. Org. Chem.* **2009**, *74*, 3566. e) F. Shibahara, E. Yamaguchi, A. Kitagawa, A. Imai, T. Murai, *Tetrahedron* **2009**, *65*, 5062. f) J. M. Crawforth, M. Paoletti, *Tetrahedron Lett.* **2009**, *50*, 4916. g) V. K. Fulwa, R. Sahu, H. S. Jena, V. Manivannan, *Tetrahedron Lett.* **2009**, *50*, 6264. h) S. Tahara, F. Shibahara, T. Maruyama, T. Murai, *Chem. Commun.* **2009**, 7009. i) V. S. Arvapalli, G. Chen, S. Kosarev, M. E. Tan, D. Xie, L. Yet, *Tetrahedron Lett.* **2010**, *51*, 284. j) A. Zhang, X. Zheng, J. Fan, W. Shen, *Tetrahedron Lett.* **2010**, *51*, 828. k) F. Shibahara, E. Yamaguchi, T. Murai, *Chem. Commun.* **2010**, *46*, 2471. l) Y. Cheng, J.-H. Peng, J.-Q. Li, *J. Org. Chem.* **2010**, *75*, 2382.

8 a) Y. Okamoto, K. Ogura, T. Kinoshita, *Polyhedron* **1984**, *3*, 635. b) K. Ogura, Y. Kurasawa, Y. Yamaguchi, Y. Okamoto, *Heterocycles* **2003**, *59*, 283.

9 O. Niyomura, Y. Yamaguchi, R. Sakao, M. Minoura, Y. Okamoto, *Heterocycles* **2008**, *75*, 297.

10 a) U. Ashauer, C. Wolff, R. Haller, *Arch. Pharm. (Weinheim, Ger.)* **1986**, *319*, 43. b) L. Goleic, I. Leban, M. Stanovinik, M. Tisler, A. Tomazic, *Croat. Chem. Acta* **1980**, *53*, 435.

11 **2**: mp 192–193 °C; IR (KBr): 3109, 3045, 1588, 1560, 1495, 1421, 1359, 1308, 1274, 1251, 1240, 1185, 1016, 952, 779, 761, 752, 738, 733, 688, 683 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.72 (ddd, $J = 7.2$, 6.5, 1.3 Hz, 2H), 6.93 (ddd, $J = 9.1$, 6.5, 0.9 Hz, 2H), 7.17 (ddd, $J = 7.5$, 4.9, 1.1 Hz, 2H), 7.75 (ddd, $J = 8.1$, 7.5, 1.8 Hz, 2H), 7.96 (d, $J = 9.1$ Hz, 2H), 8.41 (d, $J = 8.1$ Hz, 2H), 8.58 (ddd, $J = 4.8$, 1.8, 0.9 Hz, 2H), 9.90 (ddd, $J = 7.3$, 1.0, 1.0 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 114.0, 118.5, 118.9, 121.4, 121.8, 122.2, 126.3, 135.6, 135.7, 136.4, 148.0, 150.6; ^{77}Se NMR (114 MHz, $CDCl_3$): δ 145.4; UV–vis ($CHCl_3$) λ_{max} (log ε): 248 (4.39), 276 (4.25), 354 (4.54); MS (EI^+) m/z: 468 (M^+), 388 ($M^+ - Se$), 307, 194, 180; HRMS (EI^+): calcd for $C_{24}H_{16}N_6{}^{80}Se$: 468.0603; found: 468.0602; Anal. Calcd for $C_{24}H_{16}N_6Se$: C, 61.67; H, 3.45; N, 17.98%. Found: C, 61.42; H, 3.53; N, 17.75%.

12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

13 **3**: mp 235–238 °C; IR (KBr): 3106, 1587, 1493, 1422, 1356, 1310, 1275, 1183, 1147, 1124, 1021, 787, 753, 741, 730, 684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (ddd, $J = 9.0$, 6.5, 1.0 Hz, 2H), 6.67 (ddd, $J = 7.0$, 6.5, 1.0 Hz, 2H), 7.06 (ddd, $J = 9.0$, 1.0, 1.0 Hz, 2H), 7.25 (ddd, $J = 7.5$, 5.0, 1.0 Hz, 2H), 7.77 (ddd, $J = 8.0$, 7.5, 2.0 Hz, 2H), 8.40 (ddd, $J = 8.0$, 1.0, 1.0 Hz, 2H), 8.65 (ddd, $J = 5.0$, 2.0, 1.0 Hz, 2H), 9.90 (ddd, $J = 7.0$, 1.0, 1.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.0, 118.2, 118.5, 122.1, 122.2, 122.5, 126.6, 136.5, 136.8, 137.7, 148.1, 150.6; ^{77}Se NMR (114 MHz, $CDCl_3$): δ 419.5; UV–vis ($CHCl_3$) λ_{max} (log ε): 248 (4.40), 350 (sh), 360 (4.57), 400 (sh); MS (EI) m/z: 548 (M^+); HRMS (FAB^+): calcd for $C_{24}H_{16}N_6{}^{80}Se_2$: 548.9850; found: 548.9855; Anal. Calcd for $C_{24}H_{16}N_6Se_2 \cdot (CHCl_3)_{0.3}$: C, 50.13; H, 2.82; N, 14.44%. Found: C, 50.20; H, 2.87, N, 14.49%.

14 More details are discussed in the Supporting Information.[12]

15 For an oxidative condensation of amine to imine, see: a) A. Grirrane, A. Corma, H. Garcia, *J. Catal.* **2009**, *264*, 138. b) S. Kodama, J. Yoshida, A. Nomoto, Y. Ueta, S. Yano, M. Ueshima, A. Ogawa, *Tetrahedron Lett.* **2010**, *51*, 2450.

16 For a formation of diselenide by reduction of seleninic acid, see: a) L. G. Faehl, J. L. Kice, *J. Org. Chem.* **1979**, *44*, 2357. b) T. G. Back, *J. Chem. Soc., Chem. Commun.* **1981**, 530. c) D. H. R. Barton, X. Lusinchi, P. Millet, *Tetrahedron* **1985**, *41*, 4727.

17 The imine **C** was prepared in good yield from the reaction of 2-(aminomethyl)pyridine and 2-pyridinecarboxaldehyde according to the literature. C. Incarvito, M. Lam, B. Rhatigan, A. L. Rheingold, C. J. Qin, A. L. Gavrilova, B. Bosnich, *J. Chem. Soc., Dalton Trans.* **2001**, 3478.

18 In both reaction conditions, starting compound **1** was recovered. See Supporting Information for details.[12]

19 There was no exchange between **2** and **3** under ethanol or water reflux. See Supporting Information for details.[12]

20 Selected bond distances, angles, and torsion angles are listed in Tables on Supporting Information. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication Nos. CCDC-808608 for **2** and CCDC-808609 for **3**. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

21 Normal diorgano diselenides have torsion angles in the range of 74 to 87°. T. G. Back, P. W. Codding, *Can. J. Chem.* **1983**, *61*, 2749. For example: 82.5° for $(PhSe)_2$: R. Marsh, *Acta Crystallogr.* **1952**, *5*, 458. For example: 84.3° for $(2\text{-}PySe)_2$: C. O. Kienitz, C. Thöne, P. G. Jones, *Inorg. Chem.* **1996**, *35*, 3990.

22 The ^{1}H NMR spectra in $CDCl_3$ for **3** showed higher magnetic field shifts for the two protons on six-membered ring of imidazo[1,5-*a*]pyridine (7-H and 8-H, see Supporting Information[12]) than the corresponding protons of **2** (Δ 0.32 and 0.90 ppm, respectively). This may indicate that the structure of **3** in the solution is favorable to have two close intramolecular imidazo[1,5-*a*]pyridine planes. Similar high field shifts for arene proton were observed, see: a) A. Kakehi, S. Ito, H. Suga, T. Miwa, T. Mori, T. Fujii, N. Tanaka, T. Kobayashi, *Chem. Pharm. Bull.* **2003**, *51*, 75. b) A. Kakehi, H. Suga, T. Kato, T. Fujii, N. Tanaka, T. Kobayashi, *Chem. Pharm. Bull.* **2003**, *51*, 1246.

