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Reaction of selenium tetrabromide with ethynylpyridines

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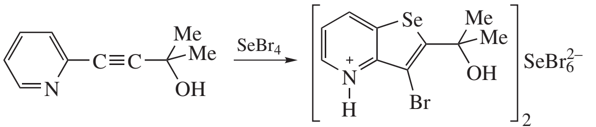
Reaction of *in situ* generated selenium(IV) bromide with substituted ethynylpyridines affords 3-bromoselenolo[3,2-*b*]pyridine or bis[(*E*)-2-bromo-2-pyridylethenyl]diselenide derivatives depending on the nature of starting reactant.

In the last decades fused pyridines have attracted considerable attention. Thienopyridine fragment can serve as a useful chromophore in potentially bioactive molecules. Substituted thienopyridine ureas are potent inhibitors of KDR kinase[1] and IκB kinase β.[2] Tricyclic thienopyridine–pyridone derivatives afforded extremely potent and selective mGluR1 antagonists.[3] However, analogous selenolopyridines are less studied and can be obtained by complicated and/or laborous methods. Unsubstituted selenolo[3,2-*b*]pyridine was synthesized by treating 3-(formylamino)selenophene[4] or *in situ* prepared 3-aminoselenophene[5] with malonaldehyde bis-acetal in the presence of zinc chloride. Substituted selenolo[3,2-*b*]pyridines were obtained by reaction of 2-cyano-3-aminoselenophenes with cyclic aliphatic ketones in the presence of $AlCl_3$ under microwave irradiation or heating.[6]

Here, aiming to develop straightforward and facile methods for the synthesis of selenolopyridines, we investigated the reaction of *in situ* prepared selenium(IV) bromide with ethynylpyridines. In the case of 2-methyl-4-(2-pyridyl)but-3-yn-2-ol **1** (Scheme 1) blood-reddish crystals were precipitated from the reaction mixture and were isolated by simple filtration. X-ray diffraction analysis of a single crystal revealed that the product was bis{3-bromo-2-(2-hydroxyprop-2-yl)seleno[2,3-*b*]pyridin-4-ium} hexabromoselenate **2**[†] (Figure 1).[‡] In the crystal structure, the doubly charged anions lie in the special positions (axis 2); the single charged cations are in general positions. Hydrogen bonds of OH···Br type between cations and anions have lengths of 3.327(5) Å [d(O–H) = 1.00 Å, d(H···Br) = 2.33 Å, ∠O–H···Br = 174°]. The other intermolecular contacts in the crystal structure correspond to sums of van der Waals radii. Apparently, $SeBr_4$ adds to a triple bond of reactant **1** at the first step of reaction. Then tribromoselenyl fragment of this adduct would attack carbon atom of the pyridine moiety at the 3-position to create the fused selenolo[2,3-*b*]pyridine system with elimination of bromine molecule (Scheme 1).



Scheme 1

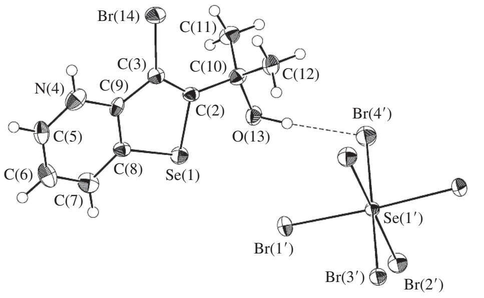
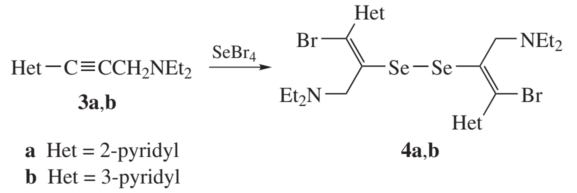


Figure 1 ORTEP molecular structure of compound **2**.

On moving to diethylaminomethyl-substituted ethynylpyridines **3a**,**b**, the reaction under the same conditions (after usual workup and routine purification by flash chromatography on silica gel) brought about non-cyclized products **4a**,**b** of bis(ethenyl)-diselenide family (Scheme 2).[§] ESI-MS, ¹H and ¹³C NMR data



Scheme 2

[†] *Synthesis of bis{3-bromo-2-(2-hydroxyprop-2-yl)selenolo[3,2-*b*]pyridin-4-ium} hexabromoselenate* **2**. A solution of 2-methyl-4-(2-pyridyl)but-3-yn-2-ol **1** (0.1 g, 0.62 mmol) in dioxane (6 ml) was added dropwise to a solution of selenium(IV) oxide (0.4 g, 3.73 mmol) in concentrated HBr (12 ml). The mixture was stirred overnight at 40 °C. After storage at room temperature for several days red crystals of compound **2** precipitated and were filtered off from the reaction mixture. Yield, 58%; mp 158–160 °C. ¹H NMR (400 MHz, DMSO-d_6) δ: 1.73 (s, 6H), 7.79 (s, 1H), 8.26 (d, 1H, J 3.2 Hz), 8.41–8.44 (m, 1H), 9.99 (d, 1H, J 3.2 Hz). ¹³C NMR (100.6 MHz, DMSO-d_6) δ: 26.7, 75.1, 93.7, 121.7, 125.0, 140.6, 142.7, 156.1, 174.5. Found (%): C, 20.19; H, 1.92; N, 2.42. Calc. for $C_{20}H_{22}Br_8N_2O_2Se_3$ (%): C, 20.04; H, 1.85; N, 2.34.

[‡] *Crystal data for compounds* **2** *and* **4a**.

Red crystals of **2** are monoclinic, space group $C2/c$, $a = 21.5992(7)$, $b = 8.7903(2)$ and $c = 16.1405(6)$ Å, $\beta = 100.532(1)°$, $V = 3012.9(2)$ Å³, $Z = 4$, $F(000) = 2216$, $\mu = 14.296$ mm^{-1}, $d_{calc} = 2.642$ g cm^{-3}, $2\theta_{max} = 55.0°$.

Yellow crystals of **4a** are monoclinic, space group $P2_1/c$, $a = 12.4661(3)$, $b = 14.6451(4)$ and $c = 15.0719(4)$ Å, $\beta = 102.4796(9)°$, $V = 2686.6(1)$ Å³, $Z = 4$, $F(000) = 1368$, $\mu = 5.75$ mm^{-1}, $d_{calc} = 1.717$ g cm^{-3}, $2\theta_{max} = 55.0°$.

A single crystal diffractometer Bruker–Nonius KappaCCD (MoKα-radiation, $\lambda = 0.71073$ Å) was used for data collection. A total of 6236 and 6139 reflections were collected at –50 and –130 °C for **2** and **4a**, respectively, using φ and ω scan technique. The structures were solved using direct method.[7] For the structure refinement, 2489 [$R_{int} = 0.057$, $I > 2\sigma(I)$] and 4224 [$R_{int} = 0.034$, $I > 3\sigma(I)$] independent reflections were used for **2** and **4a**, respectively. The final R-factors are 0.044 and 0.034 for **2** and **4a**, respectively. The SHELXS-97 and SHELXL-97 programs were used for calculations.[7]

CCDC 782370 and 782371 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2011.

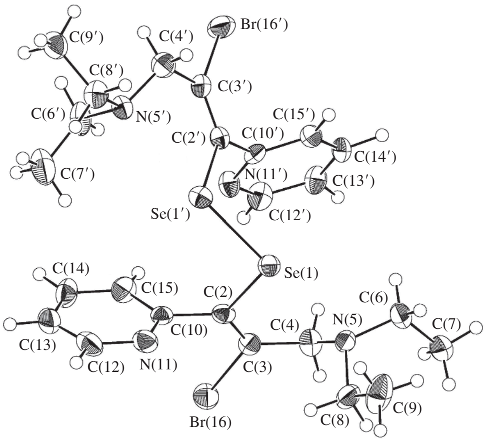


Figure 2 ORTEP molecular structure of compound **4a**.

and X-ray diffraction confirm the structures of these products.‡,§ It seems likely that the diethylaminomethyl substituent in concert with the influence of pyridine ring retards electrophilic attack of tribromoseleno group on pyridine thus preventing the cyclization. The molecular structure of **4a** with atomic numbering scheme is presented in Figure 2. In the crystal structure the molecules are not symmetrical and lie in general positions. The 1-diethylaminomethyl-2-bromo-2-pyridylethenyl fragments of this molecular structure are conformationally different: the C(2)–C(3)–C(4)–N(5) torsion angle for one of the fragments is 43.0(5)°, and it is –33.4(5)° for another fragment. The surroundings of these fragments in the crystal structure are also different: there is the shortened intermolecular contact Br(16)···C(14) [3.558(5) Å] for one of the fragments, for the second one this contact does not occur.

In summary, a very simple reaction protocol (SeO_2, HBr, dioxane, water) has been found for the direct synthesis of 3-bromoselenolo[3,2-*b*]pyridine derivative **2**, which can serve as a promising synthon in material and medicinal chemistry. Note that such a cyclization is substrate-dependent, which requires further studying of this chemistry to define its scope and limitations.

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References

1 H. R. Heyman, R. R. Frey, P. F. Bousquet, G. A. Cunha, M. D. Moskey, A. A. Ahmed, N. B. Soni, P. A. Marcotte, L. J. Pease, K. B. Glaser, M. Yates, J. J. Bouska, D. H. Albert, C. L. Black-Schaefer, P. J. Dandliker, K. D. Stewart, P. Rafferty, S. K. Davidsen, M. R. Michaelides and M. L. Curtin, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1246.

2 J.-P. Wu, R. Fleck, J. Brickwood, A. Capolino, K. Catron, Zh. Chen, Ch. Cywin, J. Emeigh, M. Foerst, J. Ginn, M. Hrapchak, E. Hickey, M.-H. Hao, M. Kashem, J. Li, W. Liu, T. Morwick, R. Nelson, D. Marshall, L. Martin, P. Nemoto, I. Potocki, M. Liuzzi, G. W. Peet, E. Scouten, D. Stefany, M. Turner, S. Weldon, C. Zimmitti, D. Spero and T. A. Kelly, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5547.

3 T. K. Sasikumar, Li Qiang, D. A. Burnett, W. J. Greenlee, Ch. Li, L. Heimark, B. Pramanik, M. Grilli, R. Bertorelli, G. Lozza and A. Reggiani, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3199.

4 F. Outurquin, G. Ah-Kow and C. Paulmier, *Bull. Soc. Chim. Fr.*, 1976, 883.

5 F. Outurquin, G. Ah-Kow and C. Paulmier, *Compt. Rend. S. C. Chim.*, 1973, **277**, 29.

6 D. Thomae, G. Kirsch and P. Seck, *Synthesis*, 2008, 1600.

7 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **A64**, 112.

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§ *Synthesis of compounds* **4a**,**b**. A solution of the reactant **3a**,**b** (0.5 g, 2.66 mmol) in dioxane (6 ml) was added dropwise to a solution of selenium(IV) oxide (0.35 g, 3.19 mmol) in concentrated HBr (10 ml). The mixture was stirred overnight at 40 °C. After keeping for two days at room temperature the mixture was treated with sodium thiosulfate and carbonate solution, then extracted with EtOAc (3 × 30 ml), the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent the products were isolated by column chromatography on silica gel using light petroleum–EtOAc (5:1) as an eluent.

*Bis[(*E*)-1-bromo-3-diethylamino-1-(2-pyridyl)prop-1-en-2-yl]diselenide* **4a**: yield, 64%; mp 130–131 °C. ESI-MS, *m/z*: 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.96 (t, 6H, *J* 7.2 Hz), 2.52 (q, 4H, *J* 7.2 Hz), 3.30 (s, 2H), 7.16–7.20 (m, 1H), 7.69 (dt, 1H, *J* 1.6 and 7.6 Hz), 8.67–8.69 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 10.9, 45.7, 62.3, 121.9, 125.9, 135.5, 149.1, 159.2. Found (%): C, 41.55; H, 4.67; N, 8.10. Calc. for $C_{24}H_{32}Br_2N_4Se_2$ (%): C, 41.52; H, 4.65; N, 8.07.

*Bis[(*E*)-1-bromo-3-diethylamino-1-(3-pyridyl)prop-1-en-2-yl]diselenide* **4b**: yield, 76%; foam. ESI-MS, *m/z*: 697. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.97 (t, 6H, *J* 7.2 Hz), 2.53 (q, 4H, *J* 7.2 Hz), 3.33 (s, 2H), 7.28–7.40 (m, 2H), 8.31–8.33 (m, 1H), 8.52 (dd, 1H, *J* 1.8 and 4.4 Hz). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 8.3, 46.8, 61.1, 107.7, 108.6, 125.1, 138.7, 145.6. Found (%): C, 41.12; H, 4.77; N, 7.91. Calc. for $C_{24}H_{32}Br_2N_4Se_2$ (%): C, 41.52; H, 4.65; N, 8.07.