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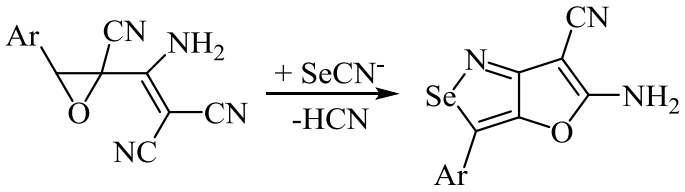

A new heterocycle: furo[3,2-*c*]isoselenazole

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Abstract — New heterocycles, furo[3,2-*c*]isoselenazoles, were obtained by the reaction of 2-[amino(2-cyano-3-aryloxiran-2-yl)methylene]malononitriles with potassium selenocyanate.

Keywords: Heterocyclic compounds; Cyano compounds; Furoisoselenazole; New heterocycle.

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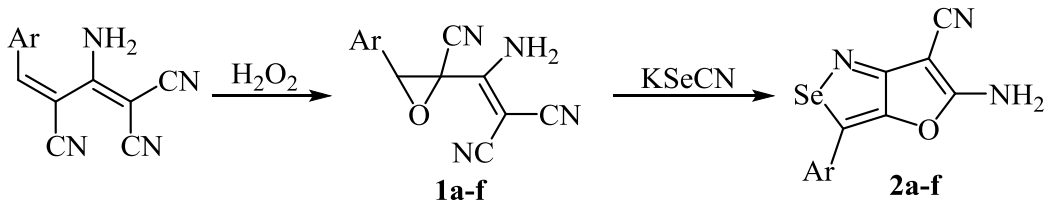
Selenorganic compounds, in particular isoselenazoles, are essential substrates in modern organic chemistry.[1] Selenazolinium salts (Se-N^+) are of interest as magnetic conducting and superconducting materials.[2] Organoselenium compounds with intramolecular nonbonding Se…N interactions have attracted interest as mimics of glutathione peroxidase (GPx) and thioredoxin reductase (TrxR).[3] Isoselenazoles, such as ebselen and its analogues, are effective anti-inflammatory and antioxidant agents.[4]

Additionally isoselenazoles are widely used intermediates in organic synthesis.[5] The reactivity of organoselenium compounds is mainly associated with the ability of selenium to stabilize adjacent positive and negative charges, as well as with the ease with which selenides to undergo oxidation to give selenoxides. Therefore, the development of preparative methods for the synthesis of selenium-containing heterocyclic is an area of continued interest. Currently, methods of synthesis of selenazoles are represented by variations of electrophilic addition of selenium-containing substrates to multiple bonds.[6]

Previously, we have described a new method for obtaining isothiazoles[7] by the reaction of thiocyanates with 2-[amino(2-cyano-3-aryloxiran-2-yl)methylene]malononitriles **1**, which were synthesized by the reaction of 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile with hydrogen peroxide.[8]

As part of our continued research, we found that no methods for the synthesis of furans which were annulated with an isoselenazole ring were reported in the literature. Therefore, based on the fact that thiocyanates and selenacyanates are isoelectronic, we extended our method to obtain 5-amino-3-arylfuro[3,2-*c*]isoselenazole-6-carbonitriles **2**.

The reaction of 2-[amino(2-cyano-3-aryloxiran-2-yl)methylene] malononitriles **1a-f** with potassium selenocyanate in a mixture of dioxane and water, led to the formation of 5-amino-3-arylfuro[3,2-*c*]isoselenazole-6-carbonitriles **2a-f** in 75-91% yields (Scheme 1, Table 1).[9]



1a-f **2a-f**

Scheme 1. Synthesis of 5-amino-3-(2-chlorophenyl)furo[3,2-*c*]isoselenazole-6-carbonitriles **2a-f.**

Table 1. Synthesis of 5-amino-3-(2-chlorophenyl)furo[3,2-*c*]isoselenazole-6-carbonitriles **2a-f.**[a]

Substrate	Ar	Product	Yield[b] (%)

1a	C_6H_5	**2a**	91
1b	2-ClC_6H_4	**2b**	85
1c	3-$NO_2C_6H_4$	**2c**	75
1d	4-FC_6H_4	**2d**	78
1e	4-$CH_3C_6H_4$	**2e**	83
1f	3-ClC_6H_4	**2f**	88

[a] Reaction conditions: compound **1 (**10 mmol), KSeCN (10 mmol), 60 °C, 1,4-dioxane (20 mL), water (20 mL).
[b] Yield of isolated product.

The structures of compounds **2a-f** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry as well as single crystal X-ray diffraction analysis of compound **2b** (Figure 1).[10]

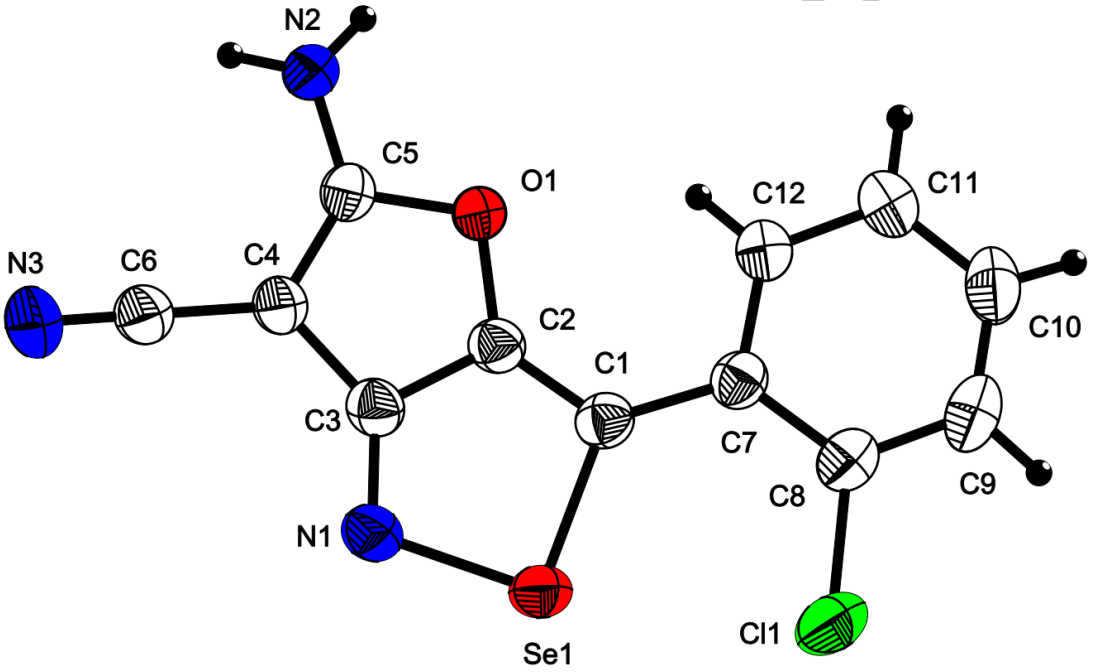
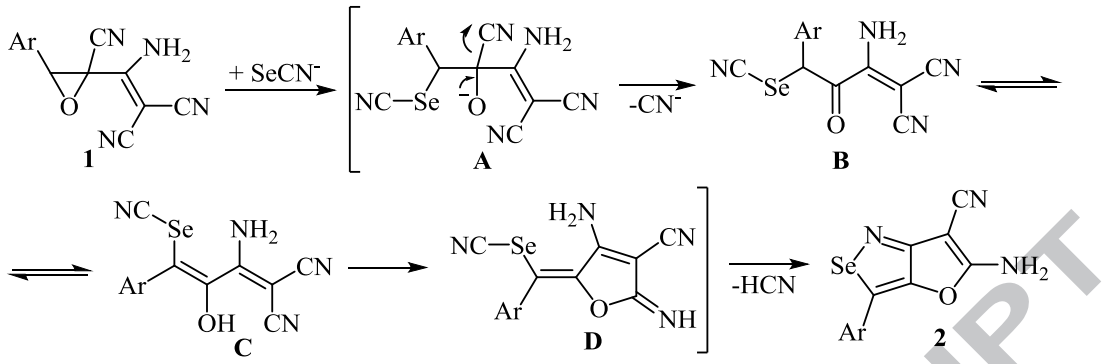


Figure 1. ORTEP diagram of 5-amino-3-(2-chlorophenyl)furo[3,2-*c*]isoselenazole-6-carbonitrile **2b**.

The obtained furo[3,2-*c*]isoselenazoles **2** are crystalline products which were stable at room temperature. Only after long-term storage in the presence of atmospheric moisture was traces of decomposition with the formation of elemental selenium observed.

Utilization of tellurocyanates for the synthesis of the analogous furo[3,2-*c*]isotellurazoles led to the formation of unstable products, that instantly decomposed with formation of elemental tellurium.

A possible mechanism for the formation of furo[3,2-*c*]isoselenazoles **2** includes the tandem formation of fused rings. It is known that the oxirane ring easily opens under the influence of various reagents. The initial ring opening of the oxirane by the selenocyanate gives cyanohydrin **A** (Scheme 2). This intermediate which is not stable in the basic medium breaks down leading to the formation of ketone **B**, which tautomerizated into enol **C**. The proximity of the hydroxy and cyano groups leads to formation of furan **D**. Next, intramolecular nucleophilic substitution of the selenium atom leads to the annulation of furan to an isoselenazole and the formation of final compound **2**.



Scheme 2. Possible mechanism for the formation of furo[3,2-*c*]isoselenazoles **2a-f**.

In conclusion, an approach to the previously undescribed heterocyclic system, including annulated furan and isoselenazole rings was developed. Novel furo[3,2-*c*]isoselenazoles **2a-f** were obtained by a simple domino process in one synthetic operation. The resulting compounds are crystalline substances that very slowly release elemental selenium, therefore they can potentially be used as a source of this biologically significant element.

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8. Golubev, R. V.; Belikov, M. Yu.; Bardasov, I. N.; Ershov, O. V.; Nasakin, O. E. *Russ. J. Org. Chem.* **2010**, *46*, 1883–1884. *Typical procedure for the preparation of* 2-(amino(3-aryl-2-cyanooxiran-2-yl)methylene)malononitrile ***1***. Hydrogen peroxide (30%) (1 mL) was added to 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile (10 mmol) in CH_3COOH (20 mL) and stirred at 80 ºC for 20 min. After cooling, H_2O (20 mL) was added, and the precipitate was filtered and washed with H_2O. Recrystallized from *i*-PrOH (5 mL).
9. *Typical procedure for the preparation of 5-amino-3-arylfuro[3,2-c]isoselenazole-6-carbonitriles **2***. 2-[Amino(2-cyano-3-aryloxiran-2-yl)methylene]malononitrile **(1)** (10 mmol) was dissolved in a solution of KSeCN (10 mmol) in a mixture of 1,4-dioxane (20 mL) and water (20 mL). The mixture was stirred at 60 °C for 1 h, cooled, filtered and washed with 1,4-dioxane (20 mL) and H_2O (20 mL). Recrystallized from 1,4-dioxane (20 mL). Compound **2e**. mp 245-246 ºC (dec.); ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 3.28 (3H, s, CH_3), 7.86 (2H, d, J = 8.43 Hz, C_6H_4), 8.05 (2H, d, J = 8.45 Hz, C_6H_4), 9.13 (2H, s, NH_2). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 43.36, 61.52, 113.71, 128.05, 128.13, 134.49, 135.38, 140.66, 140.81, 163.77, 175.63. IR (mineral oil, cm^{-1}): 3232 (NH_2), 2228 (CN). MS (EI, 70 eV): *m/z* (%) 303 $[M]^+$ (92), 183 [Ar-C-Se]$^+$ (100), 92 $[Se\text{-}CH_2]^+$ (34). Anal. Calcd for $C_{13}H_9N_3OSe$: C, 51.67; H, 3.00; N, 13.91. Found: C, 52.12; H, 6.24; N, 27.65.
10. Crystallographic data (excluding structure factors) for the structure **2b** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1446592. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]

Highlights

1. One-pot synthesis of undescribed heterocyclic system – furo[3,2-*c*]isoselenazoles.
2. New path of rearrangements of cyanooxiranes.
3. Gives the desired product in good yields under mild reaction conditions.
4. A plausible mechanism is proposed for the reaction.