Chemistry of Heterocyclic Compounds, Vol. 48, No. 9, December, 2012 (Russian Original Vol. 48, No. 9, September, 2012)

BIS-*E*-CHLOROMETHYLIDENE DERIVATIVES OF 4-THIO- AND 4-SELENOMORPHOLINAMINES

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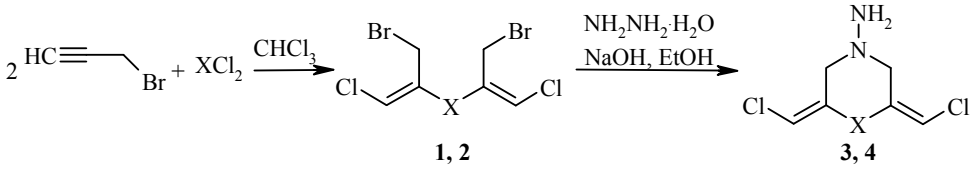
Keywords: hydrazine hydrate, propargyl bromide, selenium dichloride, 4-selenomorpholinamine, sulfur dichloride, 4-thiomorpholinamine.

It is known that the reaction of bis(2-haloethyl) sulfides with substituted amines gives 4-thiomorpholine and its *N*-substituted derivatives [1], while the reaction with hydrazine hydrate yields 4-thiomorpholinamine [1, 2]. 4-Selenomorpholinamine is unknown, but 4-selenomorpholine and a series of its *N*-substituted derivatives have been reported [3, 4].

We have developed a general method for the preparation of the previously unknown bis-*E*-chloromethylidene derivatives of 4-thiomorpholinamine **3** and 4-selenomorpholinamine **4**. The method is composed of two stages, the first of which is a stereo- and regioselective reaction of sulfur or selenium dichloride with propargyl bromide, occuring as an anti-Markovnikov addition to give the *E*,*E*-bis(3-bromo-1-chloro-1-propen-2-yl) sulfide (**1**) or selenide (**2**) in high yields [5, 6]. The second stage is a chemoselective nucleophilic substitution of the bromine atoms in the bromomethylene fragments of sulfide **1** and selenide **2** with hydrazine hydrate in the presence of NaOH to give the heterocycles **3** and **4** in high yields. This second stage includes the alkylation of one hydrazine amino group with two bromomethyl groups of the divinylchalcogenides **1** and **2**, giving the unsymmetrical 1,1-disubstituted hydrazine derivatives, which is a typical feature of the reaction between hydrazine and alkyl halides [7].



1, 2 **3, 4**

1, **3** X = S, **2**, **4** X = Se

The presence in compounds **1-4** of a =CHCl fragment is indicated by the value of the direct coupling constant ($^1J_{CH}$ = 199-203 Hz) in the ^{13}C NMR spectra, pointing to a direct carbon–halogen bond [8]. The structure of selenide **2** [5] and the 4-selenomorpholinamine **4** was also confirmed by the presence of a direct spin-spin coupling between the selenium atom and the C= carbon atom ($^1J_{C–Se}$ = 101-113 Hz) in the ^{13}C NMR spectra. The *E*,*E* configuration of the divinylchalcogenides **1** and **2**, as well as the heterocycles **3** and **4**

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1526-1528, September 2012. Original article submitted March 30, 2012.

follows from the fine structure in the ^{13}C NMR spectra characterized by a *trans*-vicinal spin-spin coupling between the vinyl proton and the carbon atom of the CH_2 group ($^3J_{CH}$ = 6.2-7.0 Hz) [9]. The ^{15}N NMR spectra of heterocycles **3** and **4** clearly reveal the signals of the two different nitrogen atoms, and in the case of the heterocycle **3** it is possible to observe the fine structure in the NH_2 ^{15}N NMR signal due to a spin-spin interaction of the nitrogen atom and proton. The mass spectra of heterocycles **3** and **4** are characterized by intensive molecular ions and the ion fragments $[M\text{-}NH_2]^+$ and $[M\text{-}Cl]^+$.

Hence the two-stage method we have discovered offers the possibility of preparing novel and promising chloromethylidene derivatives of 4-thiomorpholinamine and 4-selenomorpholinamine from the available propargyl bromide, sulfur and selenium dichlorides, and hydrazine hydrate. These are intermediate products for further functionalization, due to the presence of chlorine atoms on a double bond and free amino groups in their structure.

^1H, ^{13}C, ^{77}Se, and ^{15}N NMR spectra were recorded on a Bruker DPX-400 instrument (400, 100, 76, and 40 MHz, respectively) using $CDCl_3$ as solvent. Chemical shifts were referred to TMS (for ^1H and ^{13}C nuclei), Me_2Se (for the ^{77}Se nuclei at 0.0 ppm), or $MeNO_2$ (for the ^{15}N nuclei at 0.0 ppm). Mass spectra were recorded on a Shimadzu QP5050A instrument (EI, 70 eV) with an SPB-5ms column (60 m). Elemental analysis was carried out on a Thermo Finnigan EA 1112 analyzer.

Propargyl bromide was obtained by the bromination of propargyl alcohol using PBr_3 [10].

***E*,*E*-Bis(3-bromo-1-chloro-1-propen-2-yl) sulfide (1)** and ***E*,*E*-bis(3-bromo-1-chloro-1-propen-2-yl) selenide (2)** were prepared using methods [5, 6] in 80 and 90% yields, respectively.

(2*E*,6*E*)-2,6-Bis(chloromethylidene)thiomorpholin-4-amine (3). Sulfide **1** (0.682 g, 2 mmol) in EtOH (9 ml) was slowly added dropwise to a solution of NaOH (0.200 g, 5 mmol) in hydrazine hydrate (3.100 g, 62 mmol) at 0°C under an argon atmosphere. The mixture was stirred for 8 h at 20°C, diluted with water (9 ml), and extracted with $CHCl_3$. The extract was dried over $MgSO_4$. Solvent was removed under reduced pressure. The product obtained was purified by column chromatography on silica gel using EtOAc–$CHCl_3$ (5:95) as eluent. Yield 0.314 g (74%), a yellow oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.40 (2H, s, NH_2); 3.87 (4H, d, ^4J = 0.9, $2CH_2$); 6.27 (2H, t, ^4J = 0.9, 2 =CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 57.5 (tdt, ^1J = 140.8, ^3J = 6.3, ^3J = 4.4, $2CH_2$); 115.5 (dt, ^1J = 199, ^3J = 4.8, 2C-Cl); 128.9 (dt, ^2J = 4.0, ^2J = 4.0, C–S–C). ^{15}N NMR spectrum, δ, ppm (*J*, Hz): -315.2 (t, ^1J = 3.9, NH_2); -295.0 (s, N). Mass spectrum, *m/z* (I_{rel}, %): (^{35}Cl, ^{15}N, ^{32}S): 212 $[M]^+$ (36), 195 $[M\text{-}NH_2]^+$ (3), 177 $[M\text{-}Cl]^+$ (38), 175 (100), 158 (8), 145 (18), 131 (16), 114 (3), 92 (34), 71 (43), 69 (34), 45 (57), 39 (71). Found, %: C 34.50; H 3.91; Cl 33.86; N 13.20; S 15.54. $C_6H_8Cl_2N_2S$. Calculated, %: C 34.13; H 3.82; Cl 33.59; N 13.27; S 15.19.

(2*E*,6*E*)-2,6-Bis(*E*-chloromethylidene)selenomorpholin-4-amine (4). Compound **4** was prepared similarly to compound **3** from NaOH (0.150 g, 3.8 mmol), hydrazine hydrate (0.500 g, 10.0 mmol), and the selenide **2** (0.970 g, 2.5 mmol) in EtOH (10 ml) by stirring over 12 h and subsequent isolation by column chromatography on silica gel (eluent EtOAc–$CHCl_3$, 5:95). Yield 0.433 g (67%), a yellow oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.15 (2H, s, NH_2); 3.98 (4H, d, ^4J = 1.3, $2CH_2$); 6.38 (2H, t, ^4J = 1.3, 2 =CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 58.2 (tdt, ^1J = 140.8, ^3J = 6.2, ^3J = 4.8, $2CH_2$); 117.2 (dt, ^1J = 200.1, ^3J = 4.6, 2C-Cl); 124.4 (d, ^3J = 3.6, $^1J_{Se-C}$ = 101.0, C-Se-C). ^{77}Se NMR spectrum, δ, ppm: 404.4. ^{15}N NMR spectrum, δ, ppm (*J*, Hz): -314.2 (NH_2); -298.3 (N). Mass spectrum, *m/z* (I_{rel}, %): (^{35}Cl, ^{15}N, ^{80}Se): 260 $[M]^+$ (6), 243 $[M\text{-}NH_2]^+$ (1), 225 $[M\text{-}Cl]^+$ (9), 197 (1), 193 (4), 159 (10), 140 (8), 119 (15), 39 (100). Found, %: C 28.34; H 3.58; Cl 27.24; N 11.19; Se 30.11. $C_6H_8Cl_2N_2Se$. Calculated, %: C 27.93; H 3.13; Cl 27.48; N 10.86; Se 30.60.

This work was carried out with the financial support of the Russian Foundation for Basic Research (grant 11-03-00810-a).

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