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Short Note

1-(3-Isoselenocyanatopropyl)adamantane

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Abstract: The title compound, 1-(3-isoselenocyanatopropyl)adamantane, was synthesized for the first time from 3-(adamantan-1-yl)propan-1-amine by the two-stage reaction with 1-(3-isocyanopropyl) adamantane as intermediate. The product was characterized by NMR, GC-MS, and elemental analysis.

Keywords: adamantane; selenium; isoselenocyanate; isonitrile

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1. Introduction

Previously, we reported synthesis of adamantane isoselenocyanates containing methylene (**1**) and 1,2-ethylene (**2**) spacers between isoselenocyanate (NCSe) group and adamantane fragment [1] and selenoureas (**3**) based on them [2,3]. Isoselenocyanates and isothiocyanates with lipophilic groups possess anti-cancer activity towards triple-negative breast cancer (TNBC) cells (Figure 1) [4,5]. It was discovered that antiproliferative activity rises with the elongation of the linker between NCSe group and adamantane fragment. 1,3-Disubstituted selenoureas containing adamantane moiety show anti-inflammatory activity through the inhibition of soluble epoxide hydrolase (sEH) [6] and antioxidant activity associated with the ability of selenium to scavenge reactive oxygen species (ROS) [7,8].

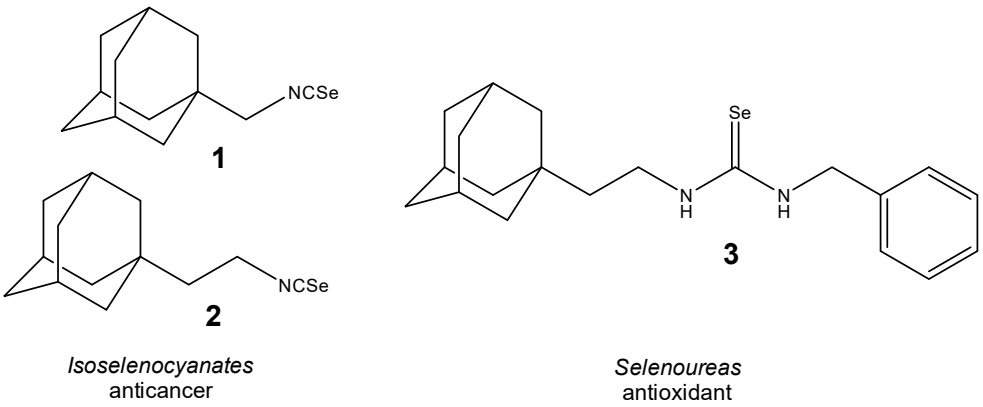


Figure 1. Bioactive adamantane compounds containing selenium. 1-(Isoselenocyanatomethyl)adamantane (**1**), 1-(2-isoselenocyanatoethyl)adamantine (**2**), and 1-(2-(adamantan-1-yl)ethyl)-3-benzylselenourea (**3**).

This makes the synthesis of new isoselenocyanates with a longer linker between the NCSe group and adamantyl moiety relevant. The present study is aimed at preparation of isoselenocyanate with a 1,3-propylene linker.

2. Results and Discussion

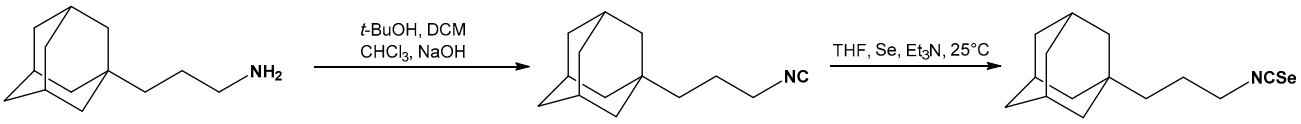
The most challenging step in preparation of isoselenocyanates is a synthesis of isonitrile from amine because of the heterogeneous nature of the reaction between $CHCl_3$ and aqueous NaOH which requires the use of phase transfer catalysts, such as Aliquat 336 or

Adogen 464 [9]. Although this approach gives good yields, it is characterized by the complexity of the isolation stage due to contamination of the product by phase transfer catalysts and its fragments. Another common method is based on the formation of formamide from the starting amine, which, in subsequent steps, is dehydrated by treatment with $POCl_3$ or triphosgene [10]. However, $POCl_3$, and, even more so, triphosgene, are highly toxic substances, the handling of which requires special care. At the same time, data on the use of alcohols for the homogenization in the reactions involving $CHCl_3$ and aqueous NaOH is described in the literature. For example, Biddle [11] recommends avoiding the use of ethyl alcohol as a solvent for KOH, and Lindemann [12] reports that without the addition of a small amount of ethyl alcohol, the reaction quickly stops. We investigated a range of alcohols, methanol, ethanol, isopropanol, *tert*-butanol, and 1-octanol, as replacements for the Aliquat 336 phase transfer catalyst. The best results have been achieved with *tert*-butanol [13]. By excluding water from the reaction, and using dry alkali, it was possible to increase the yield of isonitrile up to 88% (Table 1).

Table 1. Yield of compound **5** using alcohol as a substitute for Aliquat 336 phase transfer catalyst.

Alcohol	Time, h	The Content of Compound 5 in the Reaction Mass, %
methanol	8	23
ethanol	8	49
i-propanol	8	65
tert-butanol	8	**88**
1-octanol	8	51

We have carried out the synthesis of compound **5** in a mixture of methylene chloride and *tert*-butyl alcohol without the use of phase transfer catalysts (Scheme 1).



4 **5**, 88% **6**, 84%

Scheme 1. Synthesis of 1-(3-isoselenocyanatopropyl)adamantane (**6**) from 3-(adamantan-1-yl)propan-1-amine (**4**).

Synthesized at the first stage, 1-(3-isocyanopropyl)adamantane (**5**) has a characteristic signal in the ^{1}H NMR spectrum. The signal of $C\underline{H}_2$-NC is triplet of triplets at 3.36 ppm with J = 6.8 and 1.9 Hz (Figure S5). Spin–spin interaction between carbon-13 (^{13}C) and nitrogen-14 (^{14}N) in isonitriles can result in the splitting of carbon signals into triplets with an intensity distribution of 1:1:1. This occurs due to the symmetric distribution of electrons in the nitrogen atom, which leads to the formation of two spin states with equal energy, created when the nuclear spin of ^{14}N is oriented parallel and perpendicular to the magnetic field. Quantum transitions between these states lead to an effective spin–spin interaction between carbon and nitrogen, resulting in the splitting of carbon signals into three lines with an intensity ratio of 1:1:1. However, in some cases, due to the low concentration of isonitriles, this effect may be weak or not observed at all [14,15]. In the ^{13}C NMR spectrum, $\underline{C}H_2$-NC is a singlet at 69.16 ppm. Compound **5** was washed with water to separate *tert*-butyl alcohol and NaOH, and with 1 N HCl to remove unreacted amine **4**.

The synthesis of isoselenocyanate from isonitrile through the addition of elemental selenium occurs in a basic medium (Et_3N) at room temperature [16]. Crude compound **6** could then be isolated with 84% yield (GC-MS) by filtration of the excess of selenium and evaporation of the solvent.

3. Materials and Methods

^{1}H and ^{13}C NMR spectra were taken with a Bruker DPX 300 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA) (at frequencies of 300 and 75 MHz) in $CDCl_3$ solution with TMS as the standard. J values are given in Hz. The GC-MS spectrum was measured on an Agilent GC5975/MSD 7820 (Agilent Technologies, Santa Clara, CA, USA) using electron impact ionization (EI). Chromatographic separation was performed in splitless mode on an HP-5MS quartz capillary column (30 m × 0.25 mm × 0.5 µm film thickness) in the programmed temperature mode (from 80 to 280 °C, 10 °C/min), with carrier gas helium (1 mL/min), and at an injector temperature of 250 °C. The elemental analysis was performed on a PerkinElmer Series II 2400 Elemental Analyzer (PerkinElmer Inc., Waltham, MA, USA). The TLC analysis was carried out on Merck silica gel chromatography plates with fluorescent indicator F_{254} (1.05554); sorbent: Silica 60, layer thickness 200 um; pore size 60 Å, particle size 10–12 um; and binder: organic polymer (Merck KGaA, Darmstadt, Germany). Flash chromatography was performed on Buchi Pure C-815 Flash (Büchi Labortechnik AG, Flawil, Switzerland). The solvents and reagents were purchased from commercial sources. 3-(Adamantan-1-yl)propan-1-amine was synthesized by known methods from 1-bromoadamantane through the 3-(adamantan-1-yl)propanenitrile as intermediate [17,18].

Into a flat-bottom flask were added 364 mg (1.88 mmol, 1 eq.) of 3-(adamantan-1-yl)propan-1-amine, 5 mL of *t*-BuOH, 2.5 mL of DCM, and 301 mg (7.53 mmol, 4 eq.) of finely ground NaOH. After that, 258 mg (2.16 mmol, 1,15 eq.) of $CHCl_3$ was dissolved with 2.5 mL of DCM and added dropwise to the mixture described above with stirring. Resulting reaction mass was left stirred for 1.5 h at room temperature. After that, reaction mass was refluxed with stirring for 8 h. After cooling to room temperature, 5 mL of DCM and 5 mL of H_2O were added. The organic layer was separated, washed with 1 N HCl, and dried with Na_2SO_4. Solvent was removed in vacuo to give 338 mg (88% yield) of crude 1-(3-isocyanopropyl)adamantane (**5**, Figure 2) as yellow oil which was used further without purification. Mass spectrum, *m*/*z* (I_{rel}. %): 202 (50% $[M-1]^+$), 188 (41% $[M\text{-}CSe]^+$), 175 (48% $[M\text{-}NCSe]^+$), 160 (19% $[M\text{-}CH_2NCSe]^+$), 146 (30% $[Ad-CH_2]^+$), 135 (100% $[Ad]^+$), retention time = 13.583 min. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 1.15–1.21 (m, 2H, **H^{11}**), 1.46 (d, *J* = 2.9 Hz, 6H, **H^{2}**, **H^{8}**, **H^{9}**), 1.60–1.76 (m, 8H, **H^{4}**, **H^{6}**, **H^{10}**, **H^{12}**), 1.88–1.99 (m, 3H, **H^{3}**, **H^{5}**, **H^{7}**), 3.36 (tt, *J* = 6.8, 1.9 Hz, 2H, **H^{13}**). ^{13}C NMR (75 MHz, $CDCl_3$), δ, ppm: 22.85 (**C^{12}**), 28.61 (**C^{3}**, **C^{5}**, **C^{7}**), 31.94 (**C^{1}**), 37.09 (**C^{4}**, **C^{6}**, **C^{10}**), 41.13 (**C^{11}**), 42.31 (**C^{2}**, **C^{8}**, **C^{9}**), 69.16 (**C^{13}**). Calc. for $C_{14}H_{21}N$: C 82.70; H 10.41; N 6.89. Found: C 82.73; H 7.54.; N 4.95. M = 203.33.

Synthesis of 1-(3-isocyanopropyl)adamantane (**5**).

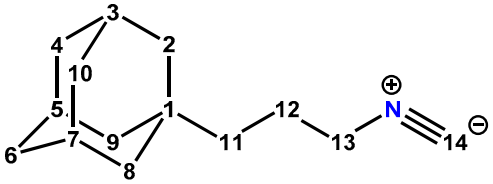


Figure 2. Carbon atoms labelling for compound **5**.

To the 338 mg (1.66 mmol, 1 eq.) of crude 1-(3-isocyanopropyl)adamantane (**5**) dissolved in 10 mL of THF were added 197 mg (2.49 mmol, 1,5 eq.) of elemental selenium and 252 uL (2.49 mmol, 1,5 eq.) of Et_3N. Reaction mass was stirred for 8 h at room temperature. The excess of selenium was separated by suction filtration and filtrate was concentrated on a rotary evaporator. The resulting crude 1-(3-isoselenocyanatopropyl)adamantane (**6**, Figure 3) was purified with flash chromatography (EA-hexane, 19-1, *v*/*v*). Pure 1-(3-isoselenocyanatopropyl)adamantane (**6**): 112 mg, 0.43 mmol, 24% yield, pale yellow oil. Mass spectrum, m/z (I_{rel}. %): 283 (18% $[M+1]^+$), 202 (9% $[M-Se]^+$), 135 (100% $[Ad]^+$), retention time = 18.239 min. ^{1}H NMR (300 MHz, $CDCl_3$), δ, ppm: 1.11–1.23 (m, 2H, **H^{11}**), 1.50 (d, *J* = 2.9 Hz, 6H, **H^{2}**, **H^{8}**, **H^{9}**), 1.59–1.80 (m, 8H, **H^{4}**, **H^{6}**, **H^{10}**, **H^{12}**), 2.03–1.95 (m, 3H, **H^{3}**, **H^{5}**, **H^{7}**), 3.58 (t, *J* = 6.8 Hz, 2H, **H^{13}**). ^{13}C NMR (DMSO-d_6), δ, ppm: 23.22 (**C^{12}**),

28.62 (**C**^{3}, **C**^{5}, **C**^{7}), 32.08 (**C**^{1}), 37.07 (**C**^{4}, **C**^{6}, **C**^{10}), 41.25 (**C**^{11}), 42.30 (**C**^{2}, **C**^{8}, **C**^{9}), 46.40 (**C**^{13}). Calc. for $C_{14}H_{21}NSe$: C 59.57; H 7.50; N 4.96. Found: 59.60; H 7.54.; N 4.95. M = 282.29.

Synthesis of 1-(3-isoselenocyanatopropyl)adamantane (**6**).

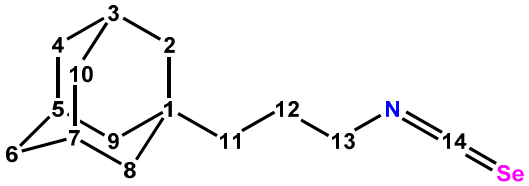


Figure 3. Carbon atoms labelling for compound **6**.

4. Conclusions

In this work, we presented the previously unknown compound 1-(3-isoselenocyanatopropyl) adamantane, which was synthesized for the first time from 3-(adamantan-1-yl)propan-1-amine by the two-stage reaction.

Supplementary Materials: The following supporting information can be downloaded online, ^{1}H NMR, ^{13}C NMR and Mass spectra; Figure S1: Chromatogram of compound **5**; Figure S2: Mass spectrum of compound **5**; Figure S3: NMR ^{1}H of compound **5**; Figure S4: Fragment of the NMR ^{1}H spectrum of compound **5** with tt of CH_2-NC; Figure S5: NMR ^{13}C of compound **5**; Figure S6: Chromatogram of compound **6**; Figure S7: Mass spectrum of compound **6**; Figure S8: NMR ^{1}H of compound **6**; and Figure S9: NMR ^{13}C of compound **6**.

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