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LETTERS TO THE EDITOR

SIMPLE SYNTHESIS OF SELENIUM-CONTAINING 1,2-DIHYDRO-2-OXONICOTINATES

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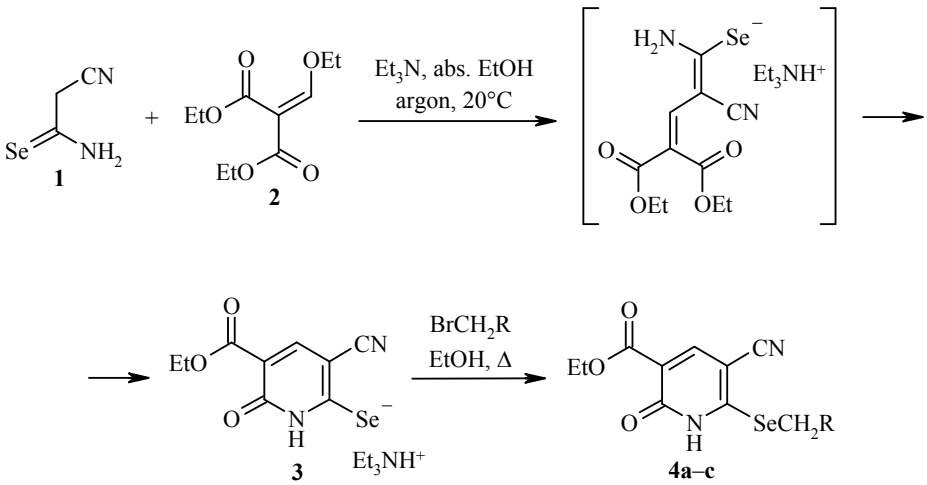
It is known that selenium-containing compounds show a unique combination of chemical properties and biological activity, and are of great practical interest (see recent reviews [1-4]). Selenoamides appear as universal building blocks for the preparation of a wide series of N,Se-containing heterocycles [5, 6]. Interest in heterocyclization reactions involving cyanoselenoacetamide (**1**) has encouraged us to study its reaction with the ethoxymethylenemalonate **2**. Ethoxymethylene compounds are quite widely used in heterocyclic synthesis as three-carbon 1,3-dielectrophilic synthons [7, 8], but only isolated examples are known of their use in preparing selenium-containing compounds [9-11]. As has been noted [9], in contrast to their sulfur-containing analogs, the preparation of Se-containing derivatives in an analytically pure state can be difficult in such reactions.



4 a R = CH_2=CH, **b** R = 4-MeC_6H_4CO, **c** R = 4-MeC_6H_4NHCO

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We have found that the cyanoselenoacetamide (**1**) can readily take part in a vinyl substitution reaction with ester **2** under mild conditions to give the previously unknown triethylammonium 3-cyano-5-ethoxycarbonyl-6-oxo-1,6-dihydropyridine-2-selenolate (**3**) in 26% yield. Attempts to optimize the method and to increase the yield of selenolate **3** were unsuccessful. Short heating of compound **3** in ethanol in the presence of alkylating agents gave the Se-alkylation products **4a-c**. It should be particularly emphasized that the 1,2-dihydro-2-oxonicotinate fragment present in the structure of compounds **3** and **4a-c** is a pharmacophore and is found in many compounds with hypoglycemic, analgesic, cytotoxic, cardiotonic, and other types of activity. We have previously shown that direct structural analogs of the synthesized compounds are inhibitors of ubiquitin C-terminal hydrolase L1 (UCH-L1) [12]. The unusual combination of oxonicotinate and selenium-containing fragments makes it highly likely that compounds **3**, **4a-c** will be found to be biologically active. At this time, work is being carried out to test the obtained compounds on biological systems.

IR spectra were recorded on an IKS-29 spectrophotometer in nujol. The ^{1}H NMR spectra were recorded on a Bruker Avance II 400 (400 MHz) instrument using DMSO-d_6 with TMS as internal standard. Elemental analysis was carried out using a Carlo-Erba 1106 instrument. Melting points were determined on a Kofler hot stage apparatus and were not corrected. Purity of the obtained compounds was monitored by TLC on Silufol UV-254 plates, eluting with acetone–hexane (1:1) and using iodine vapor and UV visualization. The cyanoselenoacetamide (**1**) was prepared by a known method [13]. All of the syntheses were carried out under an argon atmosphere.

Triethylammonium 3-Cyano-5-ethoxycarbonyl-6-oxo-1,6-dihydropyridine-2-selenolate (3). Et_3N (1.42 ml, 10.2 mmol) was added dropwise with stirring to a mixture of cyanoselenoacetamide (**1**) (1.00 g, 6.8 mmol) and diethyl ethoxymethylenemalonate (**2**) (1.66 ml, 6.8 mmol) in absolute EtOH (10 ml). The mixture was stirred for 30 min at 20°C, filtered through a fluted filter, and left for 24 h at room temperature under an argon atmosphere. The product obtained was filtered off, washed with cold EtOH and acetone. Yield 0.66 g (26%). Yellow-green, fine crystalline powder. Mp 156-158°C. IR spectrum, ν, cm^{-1}: 3390 (N–H), 2210 (C≡N), 1720, 1680 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (9H, t, ^3J = 7.2, N($CH_2C\underline{H}_3$)$_3$); 1.30 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 3.15 (6H, q, ^3J = 7.2, N($C\underline{H}_2CH_3$)$_3$); 4.15 (2H, q, ^3J = 7.1, $OC\underline{H}_2CH_3$); 7.83 (1H, s, H-4); 8.82 (1H, br. s, NH). Found, %: C 48.19, H 6.29; N 11.10. $C_{15}H_{23}N_3O_3Se$. Calculated, %: C 48.39; H 6.23; N 11.29.

Preparation of Compounds 4a-c (General Method). A mixture of selenolate **3** (150 mg, 0.40 mmol) and the corresponding alkyl halide (0.40 mmol) in 70% EtOH (1 ml) was refluxed to full dissolution of the starting reagents (over the course of 2-3 min), rapidly filtered through filter paper under an argon stream, and left for 24 h at room temperature. The precipitate formed was filtered off and washed with EtOH and hexane to give compounds **4a-c** in an analytically pure state.

Ethyl 6-(Allylseleno)-5-cyano-2-oxo-1,2-dihydropyridine-3-carboxylate (4a). Yield 90 mg (72%). White, fine crystalline powder. Mp 118-120°C. IR spectrum, ν, cm^{-1}: 3375 (N–H), 2225 (C≡N), 1691, 1672 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, ^3J = 7.0, $OCH_2C\underline{H}_3$); 3.99 (2H, d, ^3J = 7.3, $SeCH_2$); 4.28 (2H, q, ^3J = 7.0, $OC\underline{H}_2CH_3$); 5.04 (1H, d, ^3J = 9.9, CH=C$\underline{H}_2$ *cis*); 5.31 (1H, d, ^3J = 16.7, CH=C$\underline{H}_2$ *trans*); 5.93-6.04 (1H, m, C$\underline{H}$=CH_2); 8.26 (1H, s, H-4); 12.68 (1H, br. s, NH). Found, %: C 46.09; H 3.94; N 8.87. $C_{12}H_{12}N_2O_3Se$. Calculated, %: C 46.32; H 3.89; N 9.00.

Ethyl 5-Cyano-6-{[2-(4-methylphenyl)-2-oxoethyl]seleno}-2-oxo-1,2-dihydropyridine-3-carboxylate (4b). Yield 110 mg (68%). Yellow, fine crystalline powder. Mp 150-152°C. IR spectrum, ν, cm^{-1}: 3477 (N–H), 2220 (C≡N), 1695, 1680 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, ^3J = 7.0, $OCH_2C\underline{H}_3$); 2.42 (3H, s, $ArC\underline{H}_3$); 4.29 (2H, q, ^3J = 7.0, $OC\underline{H}_2CH_3$); 4.97 (2H, br. s, $SeCH_2$); 7.35 (2H, d, ^3J = 7.8, H Ar); 7.94 (2H, d, ^3J = 7.8, H Ar); 8.29 (1H, s, H-4); 12.72 (1H, br. s, NH). Found, %: C 53.46; H 4.03; N 6.86. $C_{18}H_{16}N_2O_4Se$. Calculated, %: C 53.61; H 4.00; N 6.95.

Ethyl 5-Cyano-6-({2-[(4-methylphenyl)amino]-2-oxoethyl}seleno)-2-oxo-1,2-dihydropyridine-3-carboxylate (4c). Yield 50 mg (30%). Light-grey, fine crystalline powder. Mp 193-195°C. IR spectrum, ν, cm^{-1}: 3465, 3330 (N–H), 2220 (C≡N), 1720, 1705 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.37 (3H, t,

^3J = 7.1, $OCH_2C\underline{H}_3$); 2.29 (3H, s, $ArC\underline{H}_3$); 4.11 (2H, br. s, $SeCH_2$); 4.31 (2H, q, ^3J = 7.1, $OC\underline{H}_2CH_3$); 7.04 (2H, d, ^3J = 8.4, H Ar); 7.43 (2H, d, ^3J = 8.4, H Ar); 8.23 (1H, s, H-4); 9.93 (1H, br. s, CONH); 12.72 (1H, br. s, NH). Found, %: C 51.46; H 4.12; N 9.92. $C_{18}H_{17}N_3O_4Se$. Calculated, %: C 51.68; H 4.10; N 10.05.

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