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SYNTHESIS AND REACTIONS OF 1,2-BIS[3-CYANO-4-(2-FLUOROPHENYL)-6-OXO-1,4,5,6-TETRAHYDROPYRIDIN-2-YL]DISELANE

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The interaction of 2-fluorobenzaldehyde, cyanoselenoacetamide and Meldrum's acid in the presence of N-methylmorpholine gives 1,2-bis[3-cyano-4-(2-fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridin-2-yl]diselane, which also is the product of the reaction of cyanoselenoacetamide with 5-(2-fluorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione. The diselane obtained interacts with alkyl halides in the presence of a base, forming the corresponding 4-(2-fluorophenyl)-2-(2-R-methylselanyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles.

Keywords: cyanoselenoacetamide, diselane, Meldrum's acid, 1,2,3,4-tetrahydropyridin-2-one, cyclocondensation.

Partially hydrogenated pyridine chalcogenones are a well-investigated group of heterocyclic compounds. The most studied among substituted tetrahydropyridine chalcogenones are sulfur-containing compounds [1, 2]. They display various forms of biological activity [1]. At the same time, in view of the currently limited choice of methods for obtaining substituted tetrahydropyridine selenones, they remain a little studied group of organic compounds and are represented in the literature by isolated examples [3, 4].

We have shown previously that a multicomponent reaction of aromatic aldehydes with cyanoselenoacetamide, Meldrum's acid, and *N*-methylmorpholine leads to the formation of the corresponding Michael adduct, *N*-methylmorpholinium 5-(2-cyanoethyl-1-hetaryl-2-selenocarbamoyl)-2,2-dimethyl-6-oxo-1,3-dioxa-4-cyclohexen-4-olate, which is transformed upon heating into *N*-methylmorpholinium 6-amino-4-aryl-3,5-dicyanopyridine-2-selenolate [5]. Since the sulfur-containing analogs, *N*-methylmorpholinium 5-(2-cyanoethyl-1-hetaryl-2-thiocarbamoyl)-2,2-dimethyl-6-oxo-1,3-dioxa-4-cyclohexen-4-olates under similar conditions undergo cyclocondensation with the formation of 1,2,3,4-tetrahydropyridin-2-one derivatives [2, 5, 6], we decided to study this reaction in detail.

It was established that 2-fluorobenzaldehyde (**1**) reacts with cyanoselenoacetamide (**2**) [7], Meldrum's acid (**3**), and *N*-methylmorpholine under an argon atmosphere at room temperature with the formation of Michael adduct **4**. Subsequent heating of the adduct **4** leads to a previously unknown 1,2-bis[3-cyano-4-(2-fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridin-2-yl]diselane (**5**) in 63% yield (Method A). Compound **5** may also be obtained on interacting cyanoselenoacetamide (**2**) with 5-(2-fluorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**6**)

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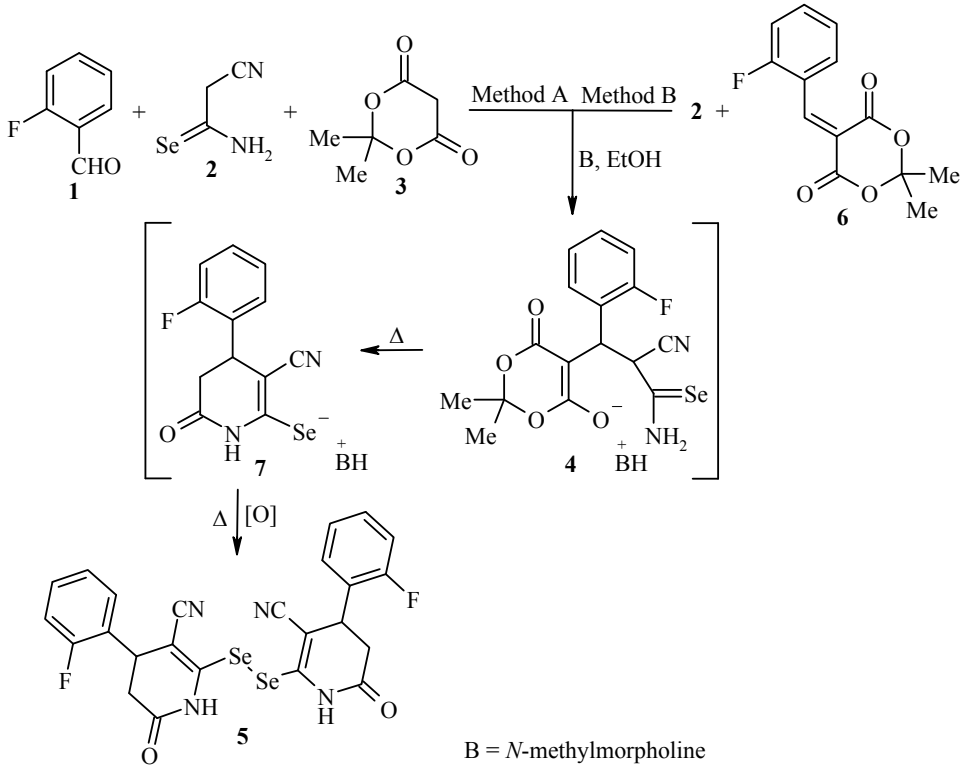
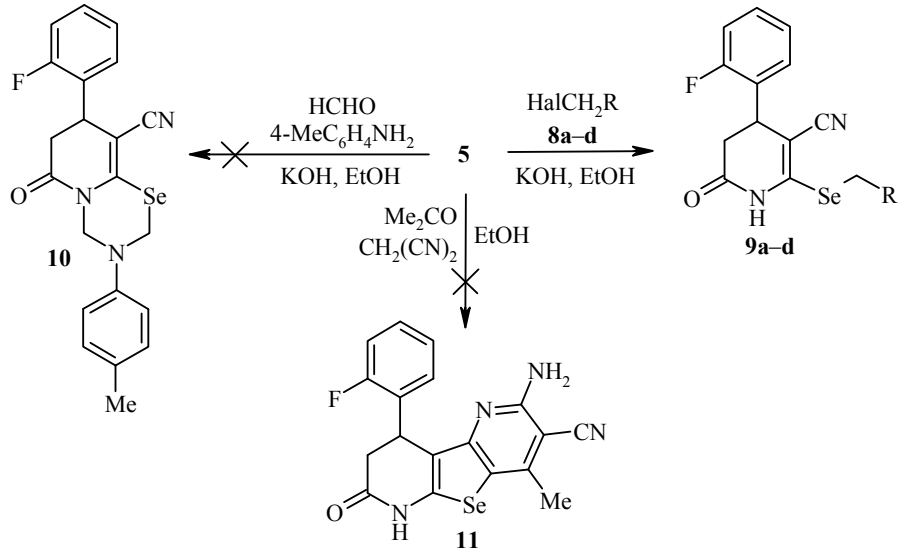
[8] in the presence of *N*-methylmorpholine in 69% yield (Method B). Cyclocondensation of the Michael adduct **4** hypothetically proceeds through the formation of *N*-methylmorpholinium 3-cyano-4-(2-fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-selenolate (**7**). Obviously, the selenolate **7** is oxidized to the stable diselane **5** in the presence of even trace amounts of oxygen (reaction proceeds under a constant stream of argon with a purity of 99.98%).



Brief heating of compound **5** with an equimolar quantity of alkyl halides **8a-d** in the presence of an excess of aqueous KOH solution led to the formation of the previously unknown 4-(2-fluorophenyl)-2-(2-R-methylselanyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles **9a-d** in 38-70% yield.



8 a Hal = I, **b** Hal = Br, **c**,**d** Hal = Cl;
8, 9 a R = Me, **b** R = 4-MeC_6H_4CO, **c** R = PhNHCO, **d** R = 4-MeC_6H_4NHCO

Attempts to obtain the selenium analog **10** of the condensed 1,3,5-thiadiazine [9, 10] by aminomethylation of the diselane **5** by the action of *p*-toluidine and HCHO were unsuccessful. Previously on interacting a series of pyridine-2-thiolates with malononitrile and acetone, we obtained a series of dipyridothiophene derivatives [11, 12]. It was established that bis(pyridin-2-yl) disulfides were involved as intermediates in this cascade reaction [13]. On attempting to obtain the dipyridoselenophene analog **11** by the reaction of diselane **5** with acetone and malononitrile, the starting diselane **5** was isolated.

The structures of compounds **5** and **9a-d** were confirmed by spectral data. In the IR spectra of compounds **5** and **9a-d**, absorption bands were present corresponding to the stretching vibrations of the functional groups in the ranges 3196-3345 (NH), 2180-2215 (CN), and 1683-1713 cm^{-1} (C=O). In the ^1H NMR spectra of compounds **5** and **9a-d**, signals of the tetrahydropyridone ring 5-CH_2 protons were detected as two double doublets in the region of 2.58-2.64 ppm (^3J = 6.0-6.1 Hz) and 2.87-2.94 ppm (^3J = 7.3-7.5 Hz), the signal of the H-4 proton appeared as a double doublet in the region of 4.19-4.24 ppm (^3J = 6.1 and 7.3-7.5 Hz), while the signal of the NH proton of the tetrahydropyridone ring was identified as a singlet in the 10.50-10.95 ppm region. A molecular ion $[M]^+$ peak with a mass of 588 was present in the mass spectrum of compound **5**.

The spectral data of compounds **9** were in good agreement with the results described in [2, 5, 6, 13-15] for the corresponding sulfur-containing analogs.

Two methods of obtaining 1,2-bis[3-cyano-4-(2-fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridin-2-yl]-diselane are proposed: 1) multicomponent condensation of cyanoselenoacetamide, Meldrum's acid, and 2-fluoro-benzaldehyde in the presence of *N*-methylmorpholine and 2) a reaction of the 2-fluorobenzylidene derivative of Meldrum's acid with cyanoselenoacetamide. The obtained diselane interacts with alkyl halides with the formation of 4-(2-fluorophenyl)-2-(2-R-methylselanyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles.

EXPERIMENTAL

The IR spectra were recorded on an IKS-29 spectrophotometer in nujol. The ^1H NMR spectra were recorded on a Bruker Avance II 400 (400 MHz) in DMSO-d_6, internal standard was TMS. HPLC-MS analysis was carried out on an Agilent 1100 liquid chromatograph with DAD, ELSD Sedex 75 detectors, connected to an Agilent LC/MSD VL mass spectrometer, ionization by electrospray. Elemental analysis was carried out on a Carlo Erba 1106 Elemental Analyzer (compounds **9c**,**d**) and a Perkin Elmer CHN Analyzer (remaining compounds). Monitoring of the purity of the obtained compounds was carried out by TLC on Silufol UV-254 plates, eluent was acetone–hexane, 1:1, visualizing with iodine vapor and a UV detector. Melting points of substances were determined on a Kofler hot stage and are not corrected. All syntheses were carried out under an argon atmosphere.

1,2-Bis[3-cyano-4-(2-fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridin-2-yl]diselane (5). A. A mixture of 2-fluorobenzaldehyde (**1**) (1.44 ml, 13.6 mmol), freshly prepared cyanoselenoacetamide (**2**) [7] (2.00 g, 13.6 mmol), and *N*-methylmorpholine (3 drops) in EtOH (30 ml) was stirred until dissolution of the starting materials, then Meldrum's acid (1.96 g, 13.6 mmol) and *N*-methylmorpholine (2.08 ml, 20.4 mmol) were added. The obtained mixture was stirred for 10 min, refluxed for 1.5 h, and stored for 72 h. The solid formed was filtered off, washed with EtOH and with hexane. The corresponding diselane **5** was obtained as fine beige crystals. Yield 2.52 g (63%).

B. A mixture of freshly prepared cyanoselenoacetamide (**2**) (1.53 g, 10.4 mmol), 5-(2-fluoro-benzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**6**) [8] (2.60 g, 10.4 mmol), and *N*-methylmorpholine (1.60 ml, 15.6 mmol) was stirred in EtOH (20 ml) for 10 min, and refluxed for 1 h. The reaction mixture was stored for 72 h. The solid formed was filtered off, washed with EtOH and hexane, and the diselane **5** (2.11 g, 69%) was obtained. The physicochemical and spectral characteristics of the compounds obtained by methods A and B were identical. Mp 141-143°C. IR spectrum, ν, cm^{-1}: 1684, 1695 (sh) (2C=O), 2180 (2C≡N), 3241 (2NH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.63 (2H, dd, ^2J = 16.4, ^3J = 6.0) and 2.93 (2H, dd, ^2J = 16.4,

^3J = 7.5, 5,5'-CH_2); 4.29-4.32 (2H, m, H-4,4'); 7.12-7.34 (8H, m, H Ar); 10.82 (2H, br. s, 2NH). Mass spectrum, *m/z* (I_{rel}, %): 588 $[M]^+$ (100). Found, %: C 48.57; H 2.77; N 9.43. $C_{24}H_{16}F_2N_4O_2Se_2$. Calculated, %: C 49.00; H 2.74; N 9.52.

4-(2-Fluorophenyl)-2-(2-R-methylselanyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles 9a-d (General Method). A mixture of diselane **5** (0.30 g, 0.5 mmol) and 10% aqueous KOH solution (0.57 ml, 1.0 mmol) was stirred until dissolution of the starting reactant (2-3 min) in 70% aq. EtOH (30 ml). Then alkyl halide **8a-d** (1 mmol) was added, the obtained solution was refluxed for 1-2 min, and rapidly filtered through a folded paper filter. The reaction mixture was stored for 24 h at 20°C. The precipitate formed was filtered off, washed with EtOH and hexane. Compounds **9a-d** were obtained in analytically pure form.

6-(Ethylselanyl)-4-(2-fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (9a). Yield 0.11 g (70%). Fine, light-yellow crystals, mp 173-175°C. IR spectrum, ν, cm^{-1}: 1683 (C=O), 2195 (C≡N), 3196 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49 (3H, t, ^3J = 7.4, $CH_2C\underline{H}_3$); 2.63 (1H, dd, ^2J = 16.4, ^3J = 6.1) and 2.90 (1H, dd, ^2J = 16.4, ^3J = 7.5, 5-CH_2); 3.12 (2H, q, ^3J = 7.4, $C\underline{H}_2CH_3$); 4.20 (1H, dd, ^3J = 6.1, ^3J = 7.5, H-4); 7.09-7.32 (4H, m, H Ar); 10.50 (1H, s, NH). Found, %: C 51.71; H 4.07; N 8.59. $C_{14}H_{13}FN_2OSe$. Calculated, %: C 52.02; H 4.05; N 8.67.

4-(2-Fluorophenyl)-2-{[2-(4-methylphenyl)-2-oxoethyl]selanyl}-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (9b). Yield 0.11 g (53%). Fine, light-gray crystals, mp 147-149°C. IR spectrum, ν, cm^{-1}: 1697 (2C=O), 2205 (C≡N), 3252 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.44 (3H, s, 4-$C\underline{H}_3C_6H_4$); 2.58 (1H, dd, ^2J = 16.4, ^3J = 6.1) and 2.87 (1H, dd, ^2J = 16.4, ^3J = 7.3, 5-CH_2); 4.19 (1H, dd, ^3J = 6.1, ^3J = 7.3, H-4); 4.69 (1H, d, ^2J = 14.2) and 4.74 (1H, d, ^2J = 14.2, $SeCH_2$); 7.11-7.92 (8H, m, H Ar); 10.54 (1H, s, NH). Found, %: C 58.64; H 4.04; N 6.62. $C_{21}H_{17}FN_2O_2Se$. Calculated, %: C 59.02; H 4.01; N 6.56.

2-[3-Cyano-4-(2-fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridin-2-ylselanyl]-*N*-phenylacetamide (9c). Yield 0.08 g (38%). Fine, white crystals, mp 179-181°C. IR spectrum, ν, cm^{-1}: 1712 (2C=O), 2204 (C≡N), 3345 (2NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.64 (1H, dd, ^2J = 16.4, ^3J = 6.1) and 2.94 (1H, dd, ^2J = 16.4, ^3J = 7.3, 5-CH_2); 3.89 (1H, d, ^2J = 13.2) and 3.95 (1H, d, ^2J = 13.2, $SeCH_2$); 4.24 (1H, dd, ^3J = 6.1, ^3J = 7.3, H-4); 7.04-7.61 (9H, m, H Ar); 10.32 (1H, s, NHPh); 10.88 (1H, s, NH). Found, %: C 55.91; H 3.80; N 9.76. $C_{20}H_{16}FN_3O_2Se$. Calculated, %: C 56.08; H 3.77; N 9.81.

2-[3-Cyano-4-(2-fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridin-2-ylselanyl]-*N*-(4-methylphenyl)-acetamide (9d). Yield 0.11 g (51%). Fine, light-gray crystals, mp 205-207°C. IR spectrum, ν, cm^{-1}: 1713 (2C=O), 2215 (C≡N), 3333 (2NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, 4-$C\underline{H}_3C_6H_4$); 2.64 (1H, dd, ^2J = 16.4, ^3J = 6.1) and 2.94 (1H, dd, ^2J = 16.4, ^3J = 7.3, 5-CH_2); 3.85 (1H, d, ^2J = 13.2) and 3.92 (1H, d, ^2J = 13.2, $SeCH_2$); 4.24 (1H, dd, ^3J = 6.1, ^3J = 7.3, H-4); 7.08 (2H, d, ^3J = 8.3) and 7.48 (2H, d, ^3J = 8.3, 4-$MeC_6\underline{H}_4$); 7.11-7.34 (4H, m, H Ar); 10.24 (1H, s, NHAr); 10.95 (1H, s, NH). Found, %: C 56.89; H 4.14; N 9.46. $C_{21}H_{18}FN_3O_2Se$. Calculated, %: C 57.02; H 4.10; N 9.50.

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