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Synthesis of linearly bonded 1,1′-bis[4-(1,3-diselenan-2-yl)pyrazoles] from 1,1′-bis(pyrazole-4-carbaldehydes) and propane-1,3-diselenol

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The reaction of linearly bonded 1,1′-bis(pyrazole-4-carbaldehydes) with propane-1,3-diselenol at room temperature in the presence of Me_3SiCl followed by treatment with triethylamine affords the corresponding 1,1′-bis[4-(1,3-diselenan-2-yl)pyrazoles].

Previously[1,2] we have shown that the interaction of linearly bonded 1,1′-bis(pyrazolecarbaldehydes) such as 1,1′-(hexane-1,6-diyl)bis(3,5-dimethyl-1*H*-pyrazole-4-carbaldehyde) and 1,1′-(benzene-1,4-diyldimethanediyl)bis(3,5-dimethyl-1*H*-pyrazole-4-carbaldehyde) with 2-mercaptoethanol (1:4 reactants ratio) in the presence of trimethylchlorosilane leads to selective formation of previously unknown corresponding bis(pyrazolyl-1,4,6-oxadithiocanes). In this reaction, each formyl group accepted two molecules of 2-mercaptoethanol followed by the heterocyclization into 1,4,6-oxadithiocanes under the action of Me_3SiCl. The reaction direction was not changed when the reactant ratio was reduced to 1:2 and the mixture of unreacted bisformylpyrazole and the corresponding bispyrazolyl-1,4,6-oxadithiocane were isolated.[1,2]

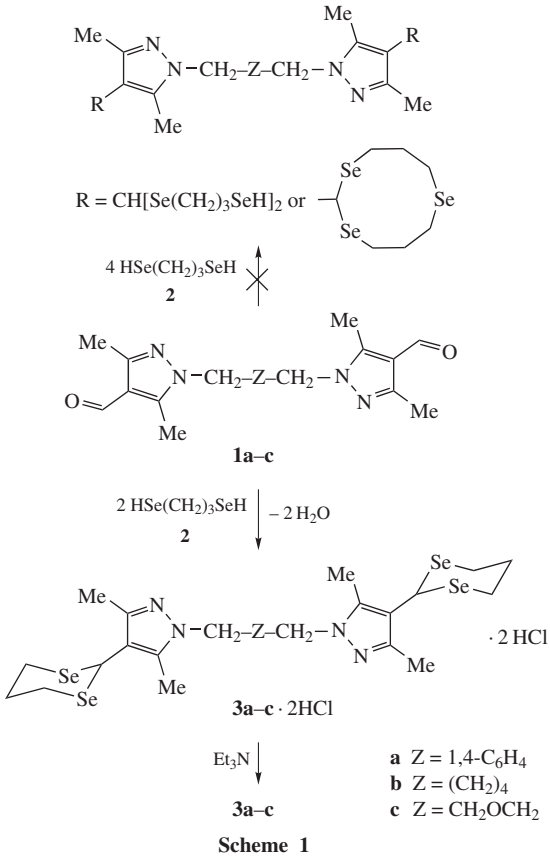
The reaction of mononuclear pyrazolecarbaldehydes with 2-mercaptoethanol in the presence of Me_3SiCl was also directed to the preferential binding of two mercaptoethanol molecules, but pyrazolyloxadithiocanes were not formed in this case.[3] For example, the reaction of pyrazolecarbaldehydes with a two-fold excess of 2-mercaptoethanol in the presence of Me_3SiCl afforded only bis(2-hydroxyethyl)dithioacetals.[3] The optimized reaction of pyrazolecarbaldehydes and 2-mercaptoethanol, performed under the conditions of aryloxathiolanes synthesis from nitrobenzaldehydes (equimolar ratio of the reactants and four-fold molar excess of Me_3SiCl at room temperature),[4] unexpectedly resulted in the formation of hydrochlorides of open-chained bis(2-hydroxyethyl)dithioacetals with admixture of 4-(1,3-oxathiolan-2-yl)-pyrazoles (approximately 20–30%), the unreacted starting aldehyde being remained in the reaction mixture.[3] At the same time, heating of pyrazolecarbaldehydes in dichloromethane with an equimolar amount of mercaptoethanol at 40–45 °C with Me_3SiCl furnished hydrochlorides of the corresponding pyrazolyl-1,3-oxathiolane in almost quantitative yields.[3,5]

Note that on reacting with mercaptoethanol–Me_3SiCl linearly bonded bis(pyrazolecarbaldehydes) were not transformed into bispyrazolyl-1,3-oxathiolane and dithioacetals, and 1-alkyl-3,5-dimethylpyrazole-4-carbaldehyde did not give pyrazolyl-1,4,6-oxadithiocanes.[1–3,5]

In continuation of our studies of the reactions of pyrazolecarbaldehydes with bischalcogenols aimed at elucidation of the reactions direction dependence on the chalcogen atom nature and identification of the conditions for the formation of polyheterocyclic systems, in this work we have studied the reaction of bispyrazoles **1a–c** with propane-1,3-diselenol **2** in the medium of Me_3SiCl.

Until our works, the reactions of heteryl- and arylcarbaldehydes with diselenols were not systematically studied due to inaccessibility and instability of diselenols. Only sporadic syntheses of 4,6-disubstituted 1,3-diselenanes (55–78% yields) *via* the reaction of 1,3-diselenols (prepared by the reduction of 1,3-diselenocyanates) with benzaldehyde and acetaldehyde in the presence of 0.5–1 equiv. $ZnCl_2$ were reported.[6] Under similar conditions, diselenanes were obtained from acetophenone and 4-*tert*-butylcyclohexanone.[7] However, this approach appeared to be inefficient for other aromatic aldehydes and sterically hindered ketones.

The reactions of bispyrazoles **1a–c** with diselenol **2** in Me_3SiCl medium were carried out under optimal conditions to obtain oxadithiocanes from bispyrazolecarbaldehydes **1a**,**b** and mercaptoethanol,[1,2] and also bis(2-hydroxyethyl)dithioacetals of pyrazole series (Scheme 1).[3] The formation of open-chained bis(3-hydro-



Scheme 1

selanylpropyl)diselenoacetals of pyrazole series or the corresponding bis(pyrazolyl-1,3,7-triselenecanes) were not observed in this reaction.

Under optimal conditions of bispyrazolyl-1,4,6-oxadithiocanes synthesis, 1,3-diselenanes **3a–c**·2HCl were isolated in a moderate yield (~40%), and 1,2-diselenolane was formed in significant amount.[8] To avoid the oxidation of diselenol **2** to 1,2-diselenolane,[8] the reaction was performed in inert medium without heating. Under the conditions of bis(2-hydroxyethyl)dithioacetals of pyrazole series[3] synthesis (aldehyde : mercaptoethanol ratio was 1:2 at room temperature in four-fold excess of Me_3SiCl), bispyrazolecarbaldehydes **1a–c** reacted with propane-1,3-diselenol to form the previously unknown dihydrochlorides of bis(diselenanylpyrazoles) **3a–c**·2HCl (Scheme 1).

Recently, for the first time we have accomplished the synthesis of pyrazolyldiselenane from 1-allyl-3,5-dimethyl-4-pyrazolecarbaldehyde and propane-1,3-diselenol in Me_3SiCl medium. A product of dichalcogenol bis-addition across the carbonyl group of aldehyde was not detected in the reaction mixture.[9]

Note that mono- and 1,1′-bis(pyrazolecarbaldehydes) in the reaction with propane-1,3-diselenol behave similarly.[9] Apparently, two bulky molecules of diselenol cannot add at one carbonyl group due to the steric hindrance.

The synthesized dihydrochlorides **3a–c**·2HCl were converted into the corresponding free bases **3a–c** upon treatment with triethylamine. The structures of compounds **3a–c** were proved by ^{1}H, ^{13}C, ^{15}N and ^{77}Se NMR spectra and elemental analysis.† The IR spectra of compounds **3a–c**·2HCl showed a broad vibration band of NH^+ at 2500–2800 cm^{-1}, thus indicating the protonation of N^2 atom of the heterocycle.[2,3]

In conclusion, the selective method for the synthesis of previously unknown bis[4-(1,3-diselenan-2-yl)pyrazoles], potential biologically active compounds,[10,11] precursors and reagents for the construction of complex multifunctional structures, promising complexing agents[12] has been developed.

The study of the structures of the compounds obtained was conducted with equipment of Baykal Analytical Center for Collective Use, Siberian Branch of the Russian Academy of Sciences.

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† ^{1}H, ^{13}C, ^{77}Se, ^{15}N NMR spectra were obtained on a Bruker DRX-400 instrument (400.13, 100.62, 76.31 and 40.56 MHz, respectively) for $CDCl_3$ solutions using HMDS (^{1}H, ^{13}C), Me_2Se (^{77}Se) and $MeNO_2$ (^{15}N) as internal standards. IR spectra were recorded on a Bruker Vertex 70 spectrometer.

Bis(pyrazole-4-carbaldehydes) **1a–c** were synthesized as described,[2] their constants (**1a**,**b**) correspond to the literature data, pyrazolecarbaldehyde **1c** was prepared by formylation of 1,1′-(oxydiethane-2,1-diyl)bis(3,5-dimethyl-1*H*-pyrazole), mp 126–128 °C [lit.,[12] 120–123 °C (C_6H_6)].

*1,1′-(Benzene-1,4-diyldimethylene)bis[3,5-dimethyl-4-(1,3-diselenan-5-yl)-1*H*-pyrazole]* **3a**. Under argon barbotage and stirring trimethylchlorosilane (0.435 g, 4 mmol) was poured to dialdehyde **1a** (0.35 g, 1 mmol) solution in CH_2Cl_2 (2 ml), then the solution of propane-1,3-diselenol **2** (0.404 g, 2 mmol) in CH_2Cl_2 (1 ml) was added with a syringe. The reaction was carried out at vigorous stirring at room temperature for 2 h. The reaction mixture was concentrated under low pressure, and the resulting product as hydrochloride was treated with Et_3N (0.202 g, 2 mmol) in CH_2Cl_2 (2 ml) and then purified on silica gel column (eluent: Et_2O). Yield 0.387 g (54%), mp 209–210 °C. IR (KBr, ν/cm^{-1}): 2918, 2888, 1554, 1469, 1431, 1417, 1386, 1317, 1241, 1104, 887, 853, 786, 754, 726. ^{1}H NMR, δ: 2.00 (dtt, 2H, H$^{5'ax}$, $^2J_{5'ax,5'eq}$ = 12.6 Hz, $^3J_{5'ax,4'ax}$ = $^3J_{5'ax,6'ax}$ = = 14.4 Hz, $^3J_{5'ax,4'eq}$ = $^3J_{5'ax,6'eq}$ = 2.3 Hz), 2.18 (dtt, 2H, H$^{5'eq}$, $^2J_{5'eq,5'ax}$ = 12.6 Hz, $^3J_{5'eq,4'eq}$ = $^3J_{5'eq,6'eq}$ = 4.4 Hz, $^3J_{5'eq,4'ax}$ = $J_{5'eq,6'ax}$ = 2.5 Hz), 2.25 (s, 6H, Me-5), 2.31 (s, 6H, Me-3), 2.84 (ddd, 4H, H$^{4'}$, H$^{6'eq}$, $^2J_{4'ax,4'eq}$ = $^2J_{6'ax,6'eq}$ = = 13.7 Hz, $^3J_{4'eq,5'ax}$ = $^3J_{6'eq,5'ax}$ = 2.3 Hz, $^3J_{4'eq,5'eq}$ = $^3J_{6'eq,5'eq}$ = 4.4 Hz), 3.09 (ddd, 4H, H$^{4'}$, H$^{6'ax}$, $^2J_{4'ax,4'eq}$ = $^2J_{6'ax,6'eq}$ = 13.7 Hz, $^3J_{4'ax,5'ax}$ = = $^3J_{6'ax,5'ax}$ = 14.4 Hz, $^3J_{4'ax,5'eq}$ = $^3J_{6'ax,5'eq}$ = 2.3 Hz), 5.12 (s, 4H, NCH_2), 5.43 (s, 2H, H$^{2'}$), 6.98 (s, 4H, Ph). ^{13}C NMR, δ: 10.54 (Me-5), 12.43 (Me-3), 18.69 (C$^{2'}$, $^1J_{Se-C}$ = 73.6 Hz), 25.24 (C$^{5'}$), 25.64 (C$^{4'}$, C$^{6'}$, $^1J_{Se-C}$ = 63.1 Hz), 52.53 (NCH_2), 116.05 (C^4), 127.09 (CH, Ar), 136.36 (C^i), 137.82 (C^5), 146.02 (C^3). ^{15}N NMR, δ: –193.0 (N^1), –98.9 (N^2). ^{77}Se NMR, δ: 348.3 (dd, $^2J_{Se,H^{4eq}}$ = $^2J_{Se,H^{6'eq}}$ = 30.6 Hz, $^3J_{Se,H^{5'eq}}$ = 9.6 Hz). Found (%): C, 43.64; H, 4.79; N, 7.83; Se, 43.74. Calc. for $C_{26}H_{34}N_4Se_4$ (%): C, 43.47; H, 4.77; N, 7.80; Se, 43.96.

*1,1′-(Hexane-1,6-diyl)bis[3,5-dimethyl-4-(1,3-diselenan-5-yl)-1*H*-pyrazole]* **3b** was prepared analogously to **3a** and purified by column chromatography on silica gel (eluent: $CHCl_3$–MeOH, 30:1). Yield 0.432 g (62%), light brown oil. IR (neat, ν/cm^{-1}): 2928, 2856, 1669, 1555, 1486, 1470, 1433, 1386, 1320, 1244, 1228, 1123, 980, 876, 843, 750, 726, 663. ^{1}H NMR, δ: 1.28 (m, 4H, CH_2CH$_2$CH$_2$N), 1.72 (m, 4H, CH$_2$CH_2CH$_2$N), 1.99 (dtt, 2H, H$^{5'ax}$, $^2J_{5'ax,5'eq}$ = 12.8 Hz, $^3J_{5'ax,4'ax}$ = $^3J_{5'ax,6'ax}$ = 14.6 Hz, $^3J_{5'ax,4'eq}$ = $^3J_{5'ax,6'eq}$ = 2.5 Hz), 2.18 (m, 2H, $H_{5'eq}$), 2.27 (s, 6H, Me-3), 2.30 (s, 6H, Me-5), 2.83 (ddd, 4H, H$^{4'}$, H$^{6'eq}$, $^2J_{4'eq,4'ax}$ = $^2J_{6'eq,6'ax}$ = 13.6 Hz, $^3J_{4'eq,5'ax}$ = $^3J_{6'eq,5'ax}$ = 2.5 Hz, $^3J_{4'eq,5'eq}$ = $^3J_{6'eq,5'eq}$ = 4.3 Hz), 3.08 (ddd, 4H, H$^{4'}$, H$^{6'ax}$, $^2J_{4'ax,4'eq}$ = $^2J_{6'ax,6'eq}$ = 13.6 Hz, $^3J_{4'ax,5'ax}$ = $^3J_{6'ax,5'ax}$ = 14.6 Hz, $^3J_{4'ax,5'eq}$ = $^3J_{6'ax,5'eq}$ = 2.5 Hz), 3.86 (t, 2H, NCH_2, ^3J = 7.2 Hz), 5.42 (s, 1H, H$^{2'}$). ^{13}C NMR, δ: 10.46 (Me-5), 12.37 (Me-3), 18.86 (C$^{2'}$, $^1J_{Se-C}$ = 73.2 Hz), 25.29 (C$^{5'}$), 25.67 (C$^{4'}$, C$^{6'}$, $^1J_{Se-C}$ = 63.3 Hz), 26.44 (CH_2CH$_2$CH$_2$N), 30.15 (CH$_2$CH_2CH$_2$N), 48.84 (NCH_2), 115.21 (C^4), 137.15 (C^5), 145.41 (C^3). ^{15}N NMR, δ: –101.5 (N^2), –189.5 (N^1). ^{77}Se NMR, δ: 345.2 (dd, $^2J_{Se,H^{4'eq}}$ = $^2J_{Se,H^{6'eq}}$ = 30.0 Hz, $^3J_{Se,H^{5'eq}}$ 10.0 Hz). Found (%): C, 41.39; H, 5.52; N, 8.10; Se, 44.99. Calc. for $C_{24}H_{38}N_4Se_4$ (%): C, 41.27; H, 5.48; N, 8.02; Se, 45.22.

*1,1′-(Oxydiethane-2,1-diyl)bis[3,5-dimethyl-4-(1,3-diselenan-5-yl)-1*H*-pyrazole]* **3c** was obtained analogously, reaction time 3 h, purified by column chromatography (CH_2Cl_2–MeOH, 95:5), recrystallized from hexane. Yield 0.466 g (68%), white crystals, mp 145–148 °C. IR (KBr, ν/cm^{-1}): 2954, 2922, 2851, 1667, 1546, 1463, 1377, 1243, 1113, 1037, 804, 727. ^{1}H NMR, δ: 2.00 (dtt, 2H, H$^{5'ax}$, $^2J_{5'ax,5'eq}$ = 14.9 Hz, $^3J_{5'ax,4'ax}$ = = $^3J_{5'ax,6'ax}$ = 12.4 Hz, $^3J_{5'ax,4'eq}$ = $^3J_{5'ax,6'eq}$ = 2.5 Hz), 2.19 (dtt, 2H, H$^{5'eq}$, $^2J_{5'eq,5'ax}$ = 14.9 Hz, $^3J_{5'eq,4'ax}$ = $^3J_{5'eq,6'ax}$ = 4.9 Hz, $^3J_{5'eq,4'eq}$ = $^3J_{5'eq,6'eq}$ = = 2.4 Hz), 2.29 (s, 6H, Me-5), 2.30 (s, 6H, Me-3), 2.85 (ddd, 4H, H$^{4'}$, H$^{6'eq}$, $^2J_{4'eq,4'ax}$ = $^2J_{6'eq,6'ax}$ = 13.7 Hz), 3.10 (ddd, 4H, H4′, H$^{6'ax}$), 3.67 (t, 4H, CH_2O, ^3J = 5.4 Hz), 4.02 (t, 4H, NCH_2), 5.43 (s, 1H, H$^{2'}$). ^{13}C NMR, δ: 10.49 (Me-5), 12.38 (Me-3), 18.66 (C$^{2'}$, $^1J_{Se-C}$ = 73.6 Hz), 25.25 (C$^{5'}$), 25.65 (C$^{4'}$, C$^{6'}$, $^1J_{Se-C}$ = 63.0 Hz), 48.65 (NCH_2), 70.13 (OCH_2), 115.40 (C^4), 138.58 (C^5), 146.02 (C^3). ^{15}N NMR, δ: –84.7 (N^2), –180.6 (N^1). ^{77}Se NMR, δ: 348.3 (dd, $^2J_{Se,H^{3'eq}}$ = $^2J_{Se,H^{5'eq}}$ = 29.9 Hz, $^2J_{Se,H^{3'ax}}$ = $^2J_{Se,H^{5'ax}}$ = 10.5 Hz). Found (%): C, 39.46; H, 5.62; N, 8.82; Se, 45.15. Calc. for $C_{22}H_{34}N_4OSe_4$ (%): C, 38.50; H, 4.99; N, 8.16; Se, 46.02.