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SYNTHESIS OF A NOVEL HETEROCYCLIC SYSTEM – PYRAZOLO[5,4,3-*de*]PYRIMIDO-[4,5-*e*][1,4]DIAZEPINE

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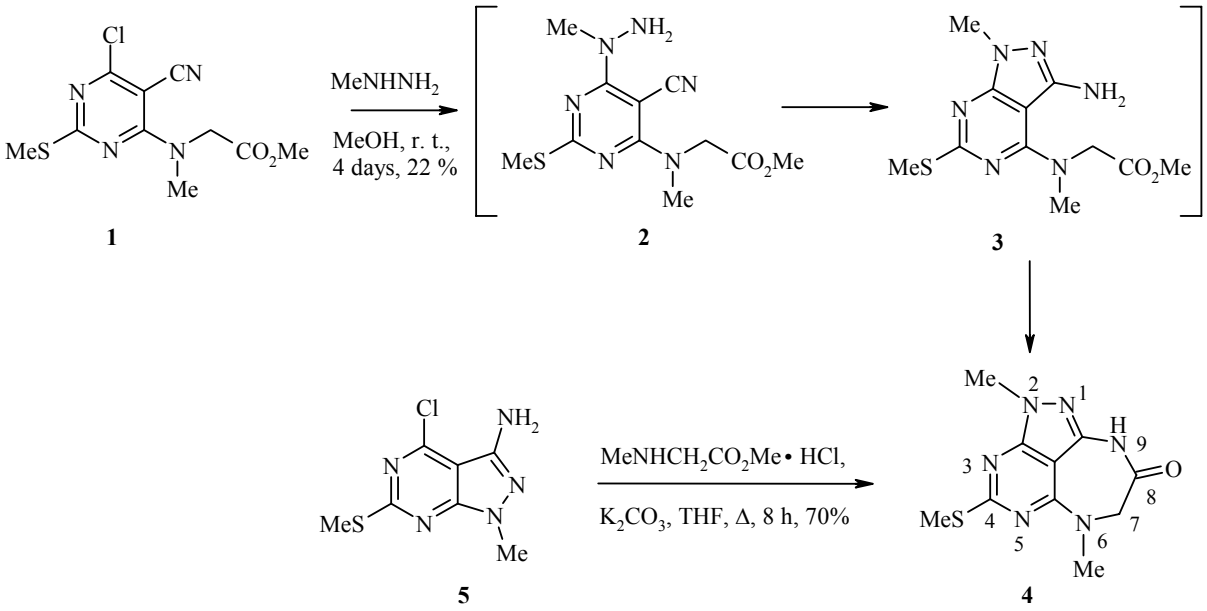
Recently, we have described the preparation of novel *ortho*-, *peri*-fused heterocycles, containing the thieno[2,3-*d*]- and pyrrolo[2,3-*d*]pyrimidine skeletons [1–4]. Continuing our work on the synthesis of fused heterocycles with anticipated biological and pharmaceutical activities in the present communication we report on a simple synthesis of novel heterosystem – pyrazolo[5,4,3-*de*]pyrimido[4,5-*e*][1,4]diazepine. The work was also stimulated by reports that some derivatives of tricyclic heterosystems containing pyrazolo-[3,4-*d*]pyrimidine moiety possess anticancer activity [5] and are useful in mixed sequence oligonucleotide primers used in DNA sequencing [6].



1 **2** **3** **4** **5**

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When N-(6-chloro-5-cyano-2-methylthio-4-pyrimidinyl)-N-methylaminoacetate (**1**) [2] was allowed to react with an excess of methylhydrazine at room temperature, formation of several compounds was observed by TLC. However, monitoring the reaction by TLC showed that some compounds formed in the beginning of the reaction disappeared over time. Full conversion of **1** was achieved after 4 days of stirring of the reaction mixture at room temperature. After isolation of the reaction product it appeared to be 2,6-dimethyl-4-methylthio-2,6,7,9-tetrahydropyrazolo[5,4,3-*de*]pyrimido[4,5-*e*][1,4]diazepin-8-one (**4**). The reaction sequence probably consists of tandem reactions including displacement of the 4-chloro group of compound **1** with methyl hydrazine, cyclization of the formed 4-(1-methylhydrazino)pyrimidine **2** to the corresponding 3-aminopyrazolo-[3,4-*d*]pyrimidine **3,** and, finally, lactam formation by the reaction of the 3-amino group of compound **3** with the ester group of the aminoacetate moiety to give tricyclic fused heterocycle **4**. Compound **4** was also synthesized by an alternate approach using the cyclocondensation reaction of 3-amino-4-chloro-1-methyl-6-methylthiopyrazolo[3,4-*d*]pyrimidine (**5**) [7] with methyl N-methylaminoacetate in the presence of potassium carbonate.

Melting points were determined in open capillaries and are uncorrected. IR spectra were run on a Perkin-Elmer FT-IR spectrophotometer Spectrum BX II in nujol. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova spectrometer (300 and 75 MHz, respectively) in DMSO-d_6, internal standart TMS. Elemental analyses were performed at the Elemental Analysis Laboratory of the Department of Organic Chemistry of Vilnius University. TLC was performed with silica gel 60 F_{254} aluminium plates (Merck).

2,6-Dimethyl-4-methylthio-2,6,7,9-tetrahydropyrazolo[5,4,3-de]pyrimido[4,5-e][1,4]diazepin-8-one (**4**). A. To a solution of compound **1** (0.20 g, 0.70 mmol) in methanol (10 ml) a solution of methylhydrazine (76 μ, 0.066 g, 1.43 mmol) in methanol (10 ml) was added dropwise. The reaction mixture was stirred at room temperature for 24 h. Then an additional amount of methylhydrazine (76 μ, 0.07g, 1.40 mmol) in methanol (10 ml) was added and the reaction mixture was stirred at room temperature for an additional 3d. The resulting solid was filtered off and recrystallized to give 0.04 g (22%) of compound **4**; mp 264-268°C (dec.) (benzene). IR pectrum, cm^{-}: 3344 (NH), 1670 (CO). ^{1}H NMR spectrum δ, ppm: 2.54 (3H, s, SCH_3); 3.19 (3H, s, N(2)–H_3); 3.75 (3H, s, N(6)–H_3); 4.20 (2H, s, CH_2); 11.23 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 14.3, 33.7, 37.0, 60.0, 91.9, 141.0, 154.1, 159.1, 167.2, 170.4. Found, %: C 45.77; H 4.99; N 32.18. $C_{10}H_{12}N_6OS$. Calculated, %: C 5.44; H 4.58; N 31.80.

B. To a solution of compound **5** (0.10 g, 0.44 mmol) in tetrahydrofuran (10 ml) methyl N-methylaminoacetate hydrochloride (0.09 g, 0.65 mmol) and K_2CO_3 (0.18 g, 1.30 mmol) was added. The reaction mixture was refluxed for 8 h. After cooling to room temperature water was added to the reaction mixture and the precipitate was filtered off and recrystallized to give 0.08 g (70%) of compound **4**, whose properties were identical to those of the product prepared by method A.

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