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Unexpected Formation of Pyrido[2,3-*d*]pyrimidine System from Simple Linear Components

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Abstract—A system of pyrido[2,3-*d*]pyrimidine series was obtained in a one-pot synthesis from diethyl ethoxymethylidenemalonic acid, cyanothioacetamide, and allyl bromide.

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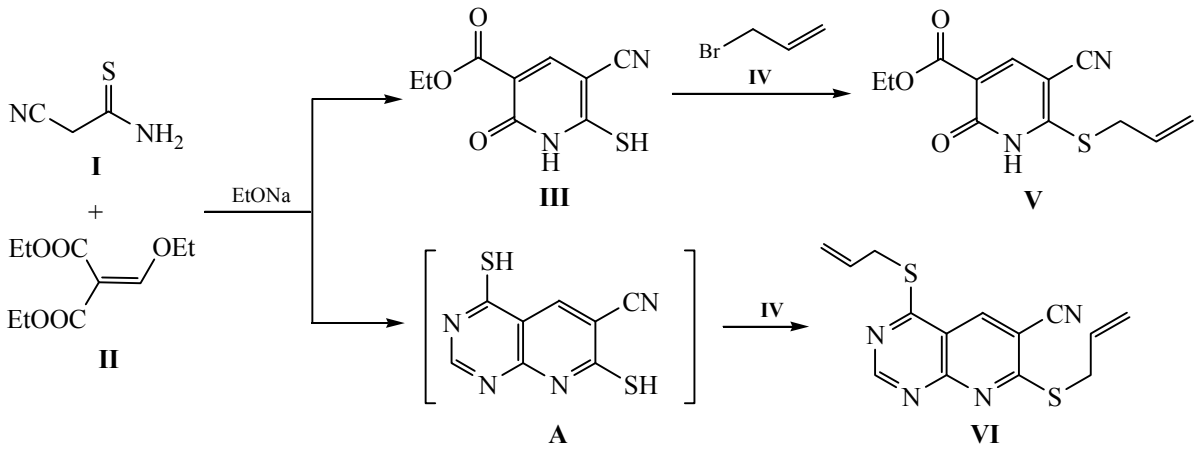
The reaction of CH-acids containing thioamide groups with ethoxymethylidenemalonates is a soft and comfortable route to mercaptopyridines [1, 2] with potential biological activity [3, 4]. The products of this reaction often contain minor impurities, which can be determined by TLC and then removed by crystallization. In order to clarify the structure of impurities and the nature of side reactions we isolated by fractional crystallization individual alkyl derivative of the by-product. NMR and mass spectral methods of structural analysis did not allow unambiguous establishing of its structure, and we performed X-ray diffraction study of this compound.

Reaction of cyanothioacetamide (**I**) and diethyl ethoxymethylidenmalonate (**II**) in the presence of excess *N*-methylmorpholine in anhydrous ethanol with the formation of *N*-methylmorfolinium salt (**III**) and its subsequent alkylation with allyl bromide (**IV**) with the formation of pyridone (**V**) has been studied previously [5]. In the present study a similar technique was used for the synthesis of compound **III**, but instead of *N*-methylmorpholine we used sodium ethoxide in anhydrous ethanol as a base, thus improving the yield of the final product. After initial isolation of the product **III** the filtrate obtained was alkylated, which led to obtaining a mixture of compounds **V** and **VI** (without isolation of the intermediate compound **A**). Further fractional crystallization allowed isolating individual product **VI**. It should be noted that obtaining pyridopyrimidine systems from simple linear reagents in one-pot synthesis has not been described previously. Obtaining such structures from the simple linear components required several stages, depending on the conditions [6, 7].

Scheme 1.



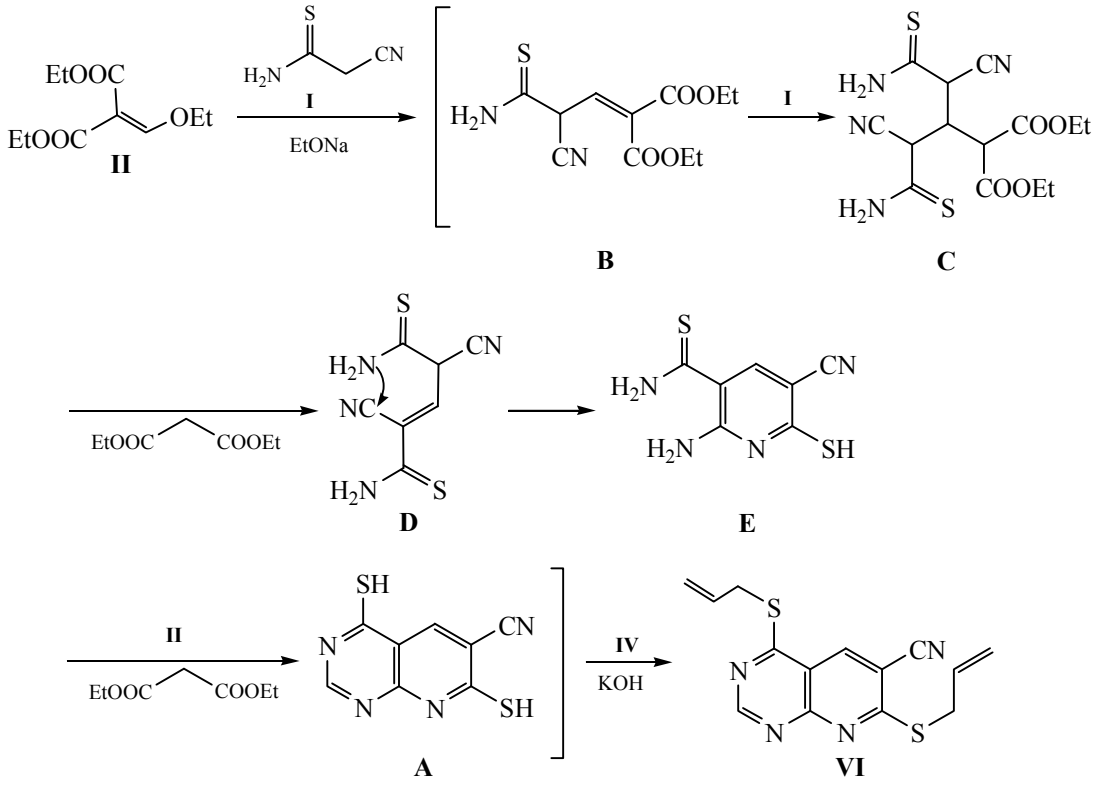
The probable reaction scheme is as follows. Cyanothioacetamid **I** attacks the methine carbon atom of diethyl ethoxymethylidenmalonate molecule **II** along S_NVin-type reaction with the formation of the intermediate **B**. The same carbon atom is then attacked by the second molecule of cyanothioacetamide **I** affording the intermediate **C**. Elimination of the malonic ester anion leads to intermediate **D**, which undergoes a closure into the pyridine ring **E**. Attack of the latter by diethyl ethoxymethylidenmalonate and cleavage of diethylmalonate leads to the formation of the system **A**, whose further alkylation with allyl bromide **IV** leads to the substituted pyridopyrimidine **VI**.

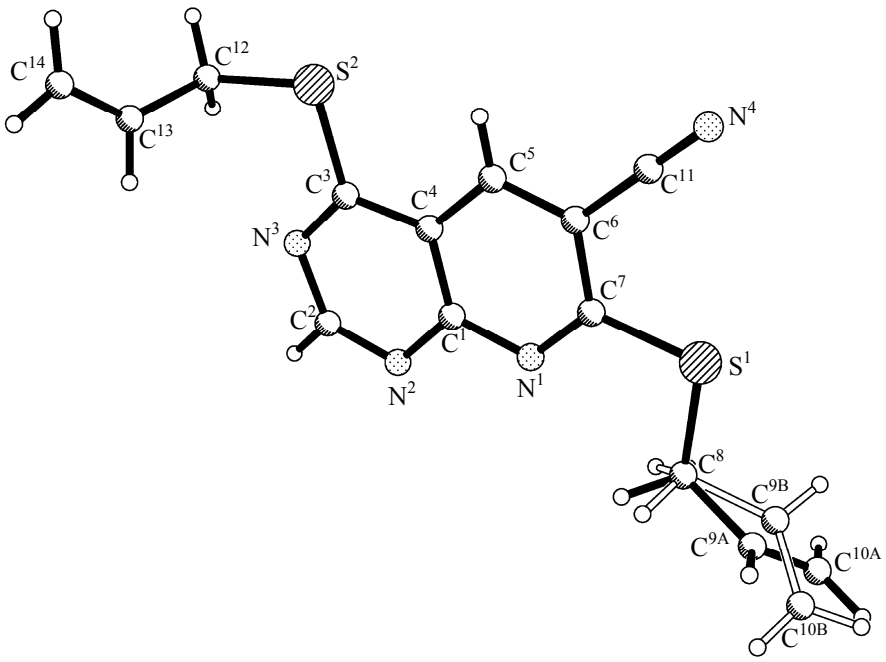
The structure of 4,7-bis(allyltio)pyrido[2,3-*d*]-pyrimidine-6-carbonitrile (**VI**) was confirmed by X-ray analysis. All non-hydrogen atoms in the molecule of compound **VI**, except for the atoms of vinyl groups, lie in one plane with an accuracy of 0.03 Å. The bonds in the bicyclic fragments are alternating, despite the aromatic nature of cycles: the bonds N^1–C^7 1.312(3) Å, N^2–C^2 1.298(3) Å, N^3–C^3 1.317(3) Å, and C^5–C^6 1.366(3) Å are somewhat shortened, while the bonds N^1–C^1 1.362(3) Å, N^2–C^1 1.361(3) Å, N^3–C^2 1.362(3) Å, C^1–C^4 1.412(3) Å, C^3–C^4 1.431(3) Å , C^4–C^5 1.397(3) Å, and C^6–C^7 1.434(3) Å are elongated compared with the average values [8] for C_{Ar}–N 1.337 Å and C_{Ar}–C_{Ar} 1.379 Å, respectively (see the figure).

The vinyl group of the substituent at the atom S^1 is disordered over two positions, **A** and **B**, with population ratio 54:46%, as a result of rotation around the bond S^1–C^8, and in the two conformers it occupies a position close to antiperiplanar [the torsion angle $C^7S^1C^8C^9$ is 159.6(5)° in conformer **A**, 168.1(5)° in conformer *B*]. The double bond C^9=C^{10} is in −*ac*-conformation relative to the S^1–C^8 in the conformer *A* and in +*ac*-conformation in conformer **B** [the torsion angle $S^1C^8C^9C^{10}$ is 107(1)° in the conformer **A**, 130(1)° in the conformer **B**]. The vinyl group of the substituent at the S^2 atom is almost perpendicular to the flat fragment of the molecule [the torsion angle $C^3S^2C^{12}C^{13}$ is 79.1(3)°], and the double bond C^{13}–C^{14} is in *ac*-conformation relative to the S^2–C^{12} [the torsion angle $S^2C^{12}C^{13}C^{14}$ is 101.1(9)°].

In the crystal the molecules of compound **VI** form layers parallel to the crystallographic plane (2–3–3). This gives rise to a short intermolecular contact $C^1\cdots S^{1'}$ (x – 1, y, z) 3.46 Å (the sum of van der Waals

Scheme 2.





Space structure of compound **VI** by X-ray analysis data.

Table 1. Coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($Å^2 \times 10^3$) of atoms in the structure **VI**

Atom	*x*	*y*	*z*	U_{eq}
S^1	6533(1)	6539(1)	1114(1)	67(1)
S^2	–2033(1)	11277(1)	2457(1)	75(1)
N^1	2731(3)	7572(2)	2517(1)	55(1)
N^2	–589(4)	8328(2)	3770(1)	64(1)
N^3	–2933(4)	10045(2)	3796(1)	64(1)
N^4	6934(5)	8512(2)	–421(2)	87(1)
C^1	899(4)	8417(2)	2918(2)	52(1)
C^2	–2357(5)	9126(2)	4132(2)	69(1)
C^3	–1487(4)	10149(2)	2981(2)	56(1)
C^4	509(4)	9322(2)	2477(2)	51(1)
C^5	2068(4)	9344(2)	1587(2)	53(1)
C^6	3896(4)	8494(2)	1181(2)	53(1)
C^7	4160(4)	7603(2)	1674(2)	53(1)
C^8	6335(6)	5698(2)	2040(3)	88(1)
C^{9A}	8725(12)	5004(7)	2007(9)	90(2)
C^{10A}	8680(30)	3879(8)	1524(10)	116(4)
C^{9B}	7840(20)	4607(8)	1533(6)	101(3)
C^{10B}	9650(20)	4167(14)	2002(12)	100(3)
C^{11}	5560(5)	8492(2)	274(2)	64(1)
C^{12}	–4514(6)	12119(3)	3374(2)	92(1)
C^{13}	–3356(10)	12881(4)	4458(3)	151(2)
C^{14}	–2760(20)	13974(6)	4853(6)	276(4)

radii [9] is 3.55 Å), which can be considered as σ-hole interaction [10, 11] between the lone electron pair of sulfur atom and the π-system of the bicyclic fragment. In the crystal also were found weak intermolecular hydrogen bonds $C^2–H^2\cdots N^{3'}$ (*–x* – 1, 2 – *y*, 1 – *z*), H···N distance 2.65 Å, C–H···N angle 148°; $C^5–H^5\cdots N^{4'}$ (1 – *x*, 2 – *y*, *–z*), H···N distance 2.56 Å, C–H···N angle 160°, and short intermolecular contact $H^{14a}\cdots C^{14'}$ (–1 – *x*, 3 – *y*, 1 – *z*) 2.82 Å (2.87 Å).

Note a specific manifestation of proton signals of allyl fragments: the *trans*-protons of the CH=CH_2 group appear as a triplet, apparently due to a superposition of two doublets, and the signal of protons of S–CH_2 is observed as a broad singlet at δ 4.05 ppm.

EXPERIMENTAL

Crystals of compound **VI** are triclinic, $C_{14}H_{12}N_4S_2$, at 20°C *a* = 5.0794(3), *b* = 12.223(1), *c* = 12.802(1) Å, α =109.206(6)°, β = 90.086(5)°, γ = 90.230(5)°, *V* = 750.58 (8) $Å^3$, M_r = 300.40, Z = 2, space group $P\bar{1}$, d_{calc} = 1,329 g cm^{-3} , μ(MoK_α) = 0.349 mm^{-1}, *F*(000) = 312. The unit cell parameters and intensities of 4274 reflections (2517 independent, R_{int} = 0.012) were measured on a diffractometer Xcalibur-3 (MoK_α-radiation, CCD detector, graphite monochromator, ω-scan, $2\theta_{max}$ = 50°).

Table 2. Bond lengths (*d*, Å) in structure **VI**

Bond	*d*	Bond	*d*
S^1–C^7	1.750(2)	S^1–C^8	1.810(3)
S^2–C^3	1.743(2)	S^2–C^{12}	1.802(3)
N^1–C^7	1.312(3)	N^1–C^1	1.362(3)
N^2–C^2	1.298(3)	N^2–C^1	1.361(3)
N^3–C^3	1.317(3)	N^3–C^2	1.362(3)
N^4–C^{11}	1.138(3)	C^1–C^4	1.412(3)
C^3–C^4	1.431(3)	C^4–C^5	1.397(3)
C^5–C^6	1.366(3)	C^6–C^7	1.434(3)
C^6–C^{11}	1.436(3)	C^8–C^{9A}	1.476(4)
C^8–C^{9B}	1.490(5)	C^{9A}–C^{10A}	1.309(5)
C^{9B}–C^{10B}	1.307(5)	C^{12}–C^{13}	1.510(4)
C^{13}–C^{14}	1.298(5)		

Table 3. Bond angles (ω, deg) in structure **VI**

Angle	ω	Angle	ω
$C^7S^1C^8$	101.5(1)	$C^3S^2C^{12}$	102.6(1)
$C^7N^1C^1$	117.9(2)	$C^2N^2C^1$	115.1(2)
$C^3N^3C^2$	115.7(2)	$N^2C^1N^1$	115.7(2)
$N^2C^1C^4$	121.4(2)	$N^1C^1C^4$	122.9(2)
$N^2C^2N^3$	129.8(2)	$N^3C^3C^4$	121.1(2)
$N^3C^3S^2$	120.6(2)	$C^4C^3S^2$	118.2(2)
$C^5C^4C^1$	118.2(2)	$C^5C^4C^3$	124.9(2)
$C^1C^4C^3$	116.9(2)	$C^6C^5C^4$	118.8(2)
$C^5C^6C^7$	119.4(2)	$C^5C^6C^{11}$	120.6(2)
$C^7C^6C^{11}$	120.0(2)	$N^1C^7C^6$	122.7(2)
$N^1C^7S^1$	120.2(2)	$C^6C^7S^1$	117.1(2)
$C^{9A}C^8S^1$	112.4(3)	$C^{9B}C^8S^1$	107.9(4)
$C^{10A}C^{9A}C^8$	121.0(1)	$C^{10B}C^{9B}C^8$	128.0(1)
$N^4C^{11}C^6$	177.9(3)	$C^{13}C^{12}S^2$	112.0(2)
$C^{14}C^{13}C^{12}$	133.6(5)		

The structure was solved by the direct methods using the program package SHELXTL [12]. At refining the structure restrictions were imposed on the bond lengths in the vinyl fragment C(sp^3)–C(sp^2) 1.51 Å, C(sp^2)–C(sp^2) 1.32 Å. The positions of the hydrogen atoms were calculated geometrically and refined using *rider* model with $U_{iso} = 1.2U_{eq}$ of the non-hydrogen atom associated with this hydrogen. The structure was refined on F^2 by full-matrix mean-square method in anisotropic approximation for non-hydrogen atoms, to $wR_2 = 0.110$ for 2426 reflections ($R_1 = 0.039$ for 1754 reflections with $F > 4\sigma(F)$, S = 0.938). Final atomic coordinates are given in Table 1, bond lengths and angles, in Tables 2 and 3, respectively.

The melting points of compounds were determined on Koeffler block. The IR spectra of the synthesized compounds were recorded on IKS-40 spectrophotometer in mineral oil. The ^{1}H NMR spectra were recorded on a Varian Mercury-500 instrument (499.9601 MHz) in a solution of DMSO-d_6 (internal reference TMS). The mass spectra were recorded on a Crommas GC/MS-Hewlett-Packard 5890/5972, with column HP-5MS (70 eV). Control over the course of the reaction and individuality of the compounds were performed by TLC on Silufol UV-254 plates, eluent a mixture acetone–hexane, 3:5, developing by iodine vapor and ultraviolet irradiation.

The initial reagents **I, II,** and **IV** were commercially available (Aldrich, 2008).

Ethyl 6-mercapto-2-oxo-5-cyano-1,2-dihydropyridine-3-carboxylate (III). 0.023 g of sodium was dissolved in 20 ml of anhydrous ethanol, 1 g of cyanothioacetamide **I** was added, and the mixture was stirred for 5 min, during which a solution was formed. Then to the reaction mixture was added 2.02 ml of diethyl ethoxymethylidenmalonate **II** and the stirring was continued for another 10 min. A precipitate was formed. The mixture was left for 2 h, the precipitate was filtered off, washed with ethanol and hexane.

Red powder, mp 305°C (MeOH–DMF). IR spectrum, ν, cm^{-1}: 1608, 1562 (δ NH), 1730 (C=O), 2234 (C≡N), 3130 (NH). ^{1}H NMR spectrum, δ, ppm: 1.21 m (3H, CH_2CH_3, ^3J 7.1 Hz), q 4.07 (2H, CH_2CH_3, ^3J 7.1 Hz), 7.83 s (1H, C^4H), 11.30 br.s (1H, NH), proton signal of the SH is not registered due to exchange with deuterium. Mass spectrum, *m/z* (I_{rel}, %): 225.03(100) $[M + 1]^+$. Found, %: C 48.05; H 3.81; N 12.28. $C_9H_8N_2O_3S$. Calculated, %: C 48.21; H 3.60; N 12.49. *M* 224.03.

The characteristics of compound **V** coincide with those described in [5].

4,7-Bis(allyltio)pyrido[2,3-*d*]pyrimidine-6-carbonitrile (VI). To the filtrate after separation of compound **III** was added 5.55 ml of 10% KOH and through a folded filterthe mixture was added to 10 mmol of allyl bromide **IV**. The solution was heated and then stirred for several hours. The brown precipitate was isolated after 1 day and crystallized successively from butanol, acetic acid, and acetone.

Red crystals, mp 115°C (from acetone). IR spectrum, ν, cm^{-1}: 2222 (C≡N). ^1H NMR spectrum, δ, ppm: 4.05 br.s (4H, S–CH_2), 5.18 d (2H, CH=CH_2, $^3J_{cis}$ 9.9 Hz), 5.41 t (2H, CH=CH_2, $^3J_{trans}$ 15.6 Hz), 5.98 m (2H, CH=CH_2), 8.99 s (1H, H_{arom}), 9.09 s (1H, H_{arom}). Mass spectrum, *m/z* (I_{rel}, %): 301.2 (100) $[M + 1]^+$. Found, %: C 55.78; H 4.09; N 18.62. $C_{14}H_{12}N_4S_2$. Calculated, %: C 55.97; H 4.03; N 18.65. *M* 300.40.

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