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SYNTHESIS AND STRUCTURE OF A NEW HETEROCYCLIC SYSTEM – 7,8-DIHYDROIMIDAZO-[1,2-*c*][1,3]THIAZOLO[4,5-*e*]PYRIMIDINE

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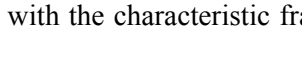
The purpose-directed synthesis of a new heterocyclic system, 7,8-dihydroimidazo[1,2-c][1,3]thiazolo[4,5-e]pyrimidine has been carried out based on the successive interaction of available 2-(aroylaminocyanomethylene)imidazolidines with hydrogen sulfide and triethyl orthoformate with subsequent intramolecular cyclocondensation of the obtained 8-aroylamino-7-thioxo-1,2,3,7-tetrahydroimidazo-[1,2-c]pyrimidines under the action of phosphorus pentasulfide or polyphosphoric acid.

Keywords: 8-aroylamino-1,2,3,7-tetrahydroimidazo[1,2-*c*]pyrimidines, phosphorus pentasulfide, polyphosphoric acid, triethyl orthoformate, heterocyclization.

N-(2-Amino-1-imidazolidin-2-ylidene-2-thioxoethyl)arylamides **1** (see Scheme), synthesized from available 2-acylamino-3,3-dichloroacrylonitriles [1], were used previously to obtain the new heterocyclic system 4,5,7,8-tetrahydroimidazo[1,2-*c*][1,3]thiazolo[4,5-*e*][1,3,2]diazaphosphinine [2].

It was shown in the present study that compounds **1** may be applied in the synthesis of one more new heterocyclic system **3**, *viz*. 7,8-dihydroimidazo[1,3-*c*][1,3]thiazolo[4,5-*e*]pyrimidine. In difference to the preparation of the 7,8-dihydroimidazo[1,2-*c*][1,3]oxazolo[4,5-*e*]pyrimidine system in [3], in the present case a different method of design of the tricyclic heterocyclic system was used, the key stage of which was not the formation of the pyrimidine ring but annelation of the five-membered ring to a tetrahydroimidazo[1,2-*c*]pyrimidine fragment. First, compounds **1a–c** were condensed with triethyl orthoformate with the formation of the previously unknown 8-aroylamino-7-thioxo-1,2,3,7-tetrahydroimidazo[1,2-*c*]pyrimidines **2a–c** (Scheme and Table 1).

Similar heterocyclizations of compounds with the characteristic fragment  were described previously in [4, 5], but the products of such reactions are as a rule monocyclic derivatives of pyrimi-

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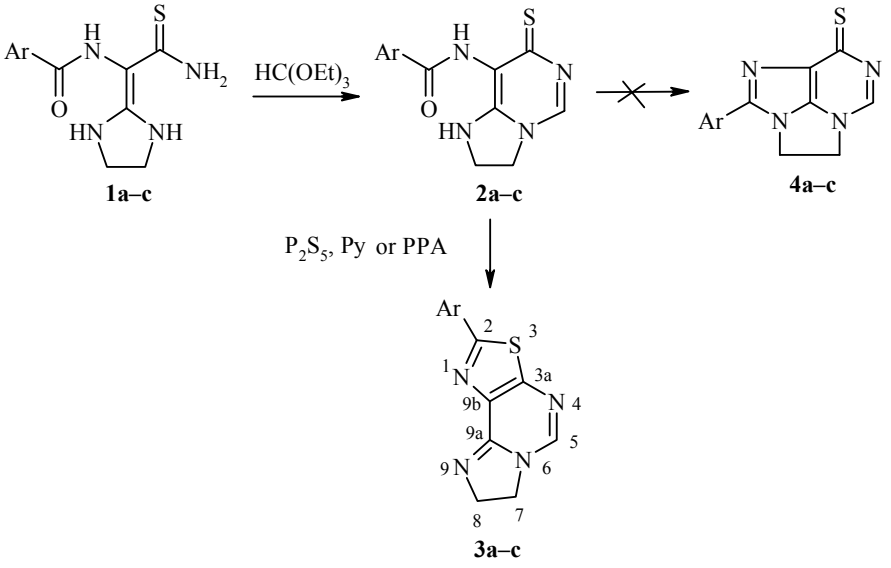
dine. Several approaches are known [6–9] for design similar bicyclic system of structure **2** but containing a 7-oxotetrahydroimidazo[1,2-*c*]pyrimidine fragment. However 7-thioxo derivatives of such structures were synthesized by us for the first time.



1–4 a Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 4-ClC_6H_4

A complex NMR analysis (NOESY, COSY, HMQC, HMBC) was carried out to confirm their structures. A complete assignment of the signals in the ^{1}H and ^{13}C spectra of compound **2a** is given in Fig. 1, and all the correlations found are given in Table 2. The large number of correlations left no doubt as to the correctness of assigning signals. Thus the presence of the imidazole fragment was confirmed by the HMBC correlation 3.81 HC(2b) → 147.03 C(8a) and 4.44 HC(3b) → 147.03 C(8a), and of pyrimidine by HMBC 8.21 HC(5b) → 186.58 CS and 8.21 HC(5b) → 147.03 C(8a). The tetrahydroimidazoline fragment is condensed with the pyrimidine as shown by the NOESY correlation 4.44 HC(3b) → 8.21 HC(5b) and HMBC 3.81 HC(2b) → 47.83 C(3b). It should be mentioned that the amide CONH bond and the imidazoline fragment are close together in space as pictured in the Scheme and in Fig. 1 and as indicated by the found NOESY correlations 8.00 HC(2,6c) → 9.61 CONH, while the NOESY interaction 7.71 HN(1b) → 9.61 CONH was not observed.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	Yield, %
		C	H	N	S		
2a	$C_{13}H_{12}N_4OS$	57.27 / 57.34	4.52 / 4.44	20.63 / 20.57	11.83 / 11.77	269–271	63
2b	$C_{14}H_{14}N_4OS$	58.79 / 58.72	4.91 / 4.93	19.50 / 19.57	11.12 / 11.20	289–290	67
2c	$C_{13}H_{11}ClN_4OS$	50.98 / 50.90	3.70 / 3.61	18.33 / 18.26	10.52 / 10.45	293–294	71
3a	$C_{13}H_{10}N_4S$	61.49 / 61.40	4.01 / 3.96	22.08 / 22.03	12.69 / 12.61	229–231	65 (A), 61 (B)
3b	$C_{14}H_{12}N_4S$	62.74 / 62.66	4.60 / 4.51	20.96 / 20.88	12.02 / 11.95	257–258	71 (A), 66 (B)
3c	$C_{13}H_9ClN_4S$	53.98 / 54.07	3.21 / 3.14	19.49 / 19.40	11.18 / 11.10	244–245	69 (A), 65 (B)

*Solvent for recrystallization was ethanol.

TABLE 2. Correlations Found in the COSY, NOESY, HMQC, and HMBC Spectra of Compound **2a***

^{1}H, δ	^{1}H, δ		^{13}C, δ	
	COSY	NOESY	HMQC	HMBC
7.61 (H-4c)	7.58	7.58	132.66	128.28 (C-2c,6c)
7.58 (H-3c,5c)	7.61, 8.00	7.61, 8.00	129.38	134.39 (C-1c), 129.38 (C-3c,5c)
8.00 (H-2c,6c)	7.58	7.58, 9.61	128.28	132.66 (C-4c), 128.28 (C-2c,6c)
9.61 (CONH)	–	8.00	–	147.03 (C-8ab), 165.20 (CO), 186.58 (C-7)
7.71 (NH)	–	3.81	–	147.03 (C-8ab), 44.03 (C-2b), 47.83 (C-3b)
3.81 (2H-2b)	4.44	7.71, 4.44	44.03	147.03 (C-8ab), 47.83 (C-3b)
4.44 (2H-3b)	3.81	3.81, 8.21	47.83	147.03 (C-8ab), 44.03 (C-2b), 141.69 (C-5b)
8.21 (H-5b)	–	4.44	141.69	147.03 (C-8ab), 44.03 (C-2b), 186.58 (C-7), 113.02 (C-8)

*Assignment of signals in compound **2a**, see Fig. 1.

Owing to the fact that compounds **2a–c** contain acylamine residues and a thioxo group in vicinal positions, intramolecular cyclization under the action of phosphorus pentasulfide or polyphosphoric acid remains a possibility. Similar reactions are well known in syntheses of thiazolopyrimidine derivatives [10–13]. It should be noted that on carrying out this reaction it is also possible to expect the formation of tricyclic structures **4a–c** with a purine fragment (see analogies in [14–18]). However in all cases only the formation of compounds **3a–c** in fairly high yields were observed (65–71%). The formation of compounds **4** was not established even with the aid of spectral monitoring of the reaction mixture. Moreover, purpose-directed attempts (heating in acetic anhydride, aqueous alcoholic alkali, formic acid, or formamide) to synthesize compounds **4** were unsuccessful.

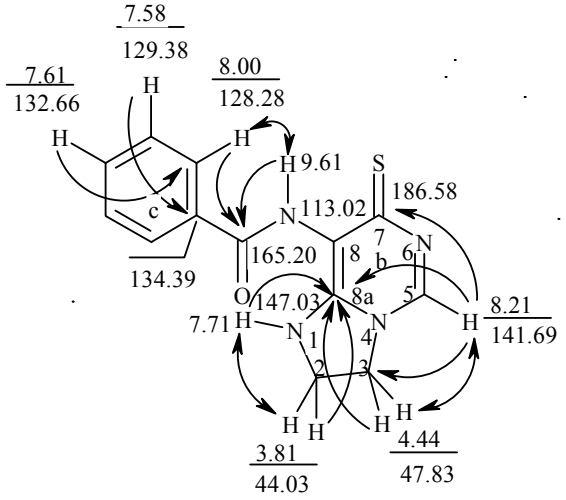


Fig. 1. Main correlations (shown by arrows) and assignment of signals (ppm) in the ^{1}H and ^{13}C NMR spectra of compound **2a**.

The absence from the ^{13}C NMR spectra (in DMSO-d_6) of a signal of the thioxo group characteristic of compounds **2** (for example for compound **2a** $\delta_{C=S}$ 186.58 ppm) indicates the structure of 7,8-dihydroimidazo[1,2-*c*][1,3]thiazolo[4,5-*e*]pyrimidines **3**. It should be mentioned that in the ^{13}C NMR spectrum of compound **3a** taken in CF_3COOD solution, a signal was present at δ 175.89 ppm (Table 3), which highly probably might also have been assigned to the C=S signal of compounds **4**. However, a detailed analysis of the spectra made us consider the possibility that in CF_3COOD solution protonation not only of the N(9) atom, but also of N(1) occurs (see Scheme) as indicated by the low field (δ 175.89 ppm) displacement of the signal of the C(3a) atom of compound **3a** (Table 3). In the IR spectra of compounds **3** also broad absorption bands for the N–H group in the 3155–3240 cm^{-1} region were absent, which were present for compounds **2**. In addition the mass spectra of compounds **3** point to the cleavage of a molecule of water in the process of conversion of **2** → **3** (Table 3).

TABLE 3. Spectral Data of the Synthesized Compounds

Compound	IR pectrum, ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)	Mass spectrum, *m/z*
2a	1644* (C=O), 3240 (NH)	3.85 (2H, t, *J* = 7.6, CH_2); 4.46 (2H, t, *J* = 7.6, CH_2); 7.52–8.00 (5H, m, H Ar); 7.68 (1H, s, NH); 8.19 (1H, s, H-2); 9.76 (1H, s, CONH)	272 $[M]^+$
2b	1644* (C=O), 3222 (NH)	2.39 (3H, s, CH_3); 3.81 (2H, t, *J* = 7.4, CH_2); 4.43 (2H, t, *J* = 7.4, CH_2); 7.40 (2H, d, *J* = 7.5, H Ar); 7.68 (1H, s, NH); 7.87 (2H, d, *J* = 7.5, H Ar); 8.20 (1H, s, H-2); 9.60 (1H, s, CONH)	286 $[M]^+$
2c	1649* (C=O), 3155 (NH)	3.80 (2H, t, *J* = 7.4, CH_2); 4.43 (2H, t, *J* = 7.4, CH_2); 7.62 (2H, d, *J* = 7.6, H Ar); 7.69 (1H, s, NH); 8.08 (2H, d, *J* = 7.6, H Ar); 8.19 (1H, s, H-2); 9.56 (1H, s, CONH)	306 $[M]^+$
3a*[2]	1660 (C=N), 3050–3500 (bands absent)	3.97 (2H, t, *J* = 9.2, CH_2); 4.16 (2H, t, *J* = 9.2, CH_2); 7.54–7.94 (5H, m, H Ar); 8.13 (1H, s, H-2)	254 $[M]^+$
3b	1662 (C=N), 3050–3500 (bands absent)	2.36 (3H, s, CH_3); 3.96 (2H, t, *J* = 9.4, CH_2); 4.15 (2H, t, *J* = 9.4, CH_2); 7.32 (2H, d, *J* = 7.5, H Ar); 7.81 (2H, d, *J* = 7.5, H Ar); 8.01 (1H, s, H-2)	268 $[M]^+$
3c	1662 (C=N), 3050–3500 (bands absent)	4.00 (2H, t, *J* = 9.4, CH_2); 4.13 (2H, t, *J* = 9.4, CH_2); 7.58 (2H, d, *J* = 7.8, H Ar); 7.94 (2H, d, *J* = 7.8, H Ar); 8.13 (1H, s, H-2)	288 $[M]^+$

*Band with shoulder.

*[2] ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 46.97 (CH_2), 54.08 (CH_2), 126.93 (C-2,6 Ph), 129.99 (C-3,5 Ph), 131.53 (C-4 Ph), 133.34, 134.20, 146.75 (C-5), 149.72, 157.64, 163.07 (C-5). ^{13}C NMR spectrum (CF_3COOD), δ, ppm: 45.87 (CH_2), 50.30 (CH_2), 128.92 (C-2,6 Ph), 130.17, 130.66 (C-3,5 Ph), 131.17, 134.91 (C-4 Ph), 145.28 (C-5), 152.26, 164.37, 175.89 (C-3a).

X-Ray structural analysis of one of the compounds **3** provided an unequivocal confirmation of the proposed structure of the final products. The general shape of the **3c** molecule is given in Fig. 2, its main bond lengths and valence angles are given in Table 4. The central tricyclic system S(1)N(1-4)C(1-7) is almost planar, the deviation of atoms from the mean square plane does not exceed 0.107 Å. The benzene ring C(8)–C(13) is practically coplanar with this system (dihedral angle was 4.6°).

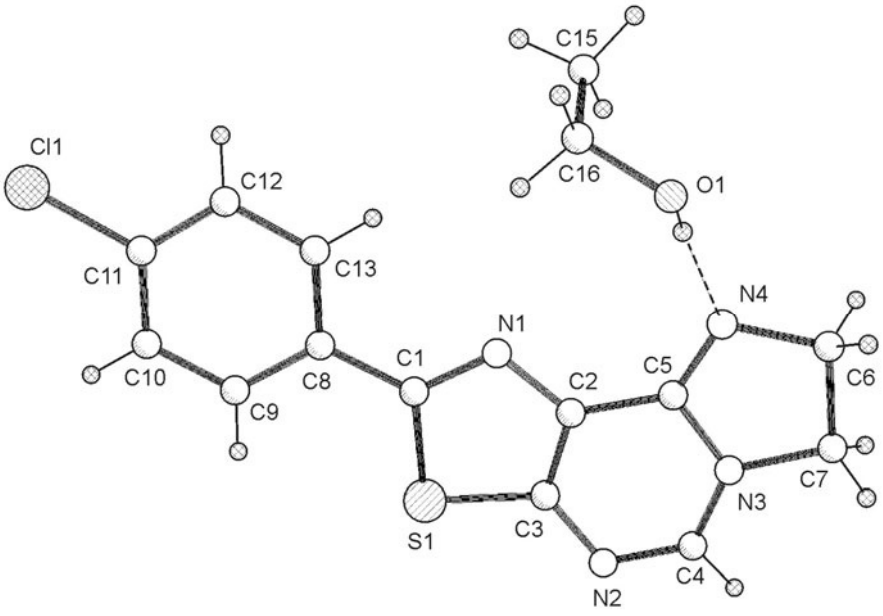


Fig. 2. General form of the compound 3c molecule.

Hence not only were new derivatives of 7-thioxotetrahydroimidazo[1,2-*c*]pyrimidines **2** synthesized, but also conditions were found for the regiospecific cyclization of the latter into representatives of a new heterocyclic system, *viz*. 7,8-dihydroimidazo[1,2-*c*][1,3]thiazolo[4,5-*e*]pyrimidine **3**.

TABLE 4. Main Bond Lengths (l) and Valence Angles (ω) of Compound **3c**

Main bond lengths	*l*, Å	Valence angles	ω, deg
S(1)–C(1)	1.747(3)	C(1)S(1)C(3)	88.81(12)
S(1)–C(3)	1.719(3)	C(1)N(1)C(2)	110.4(2)
N(1)–C(1)	1.297(3)	C(3)N(2)C(4)	113.3(2)
N(1)–C(2)	1.370(3)	C(4)N(3)C(5)	124.4(2)
N(2)–C(3)	1.376(3)	C(5)N(4)C(6)	107.2(2)
N(2)–C(4)	1.297(4)		
N(3)–C(4)	1.346(4)		
N(3)–C(5)	1.405(3)		
N(3)–C(7)	1.467(4)		
N(4)–C(5)	1.272(4)		
N(4)–C(6)	1.472(4)		
C(2)–C(3)	1.376(3)		

EXPERIMENTAL

The IR spectra of substances were recorded on a Vertex 70 spectrometer in KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 (at 300 and 75 MHz respectively) in DMSO-d_6 or CF_3COOD, and the NMR heteronuclear ^{1}H–^{13}C correlation spectra of compound **2a** were taken on a Mercury 400 (at 400 and 100 MHz respectively) in DMSO-d_6, internal standard was TMS. Chromato-mass spectra were obtained using a liquid chromato-mass spectrometric system on a high performance liquid chromatograph of the Agilent 1100 Series fitted with a diode matrix and an Agilent LC/MSD SL mass selective detector. The parameters of the chromato-mass analysis were: column Zorbax SB-C18 1.8 μm 4.6×15 mm (PN 821975-932); solvent A was acetonitrile–water, 95:5, 0.1% trifluoroacetic acid, B 0.1% aqueous trifluoroacetic acid, eluent flow rate was 3 ml/min; injection volume 1 μliter; UV detector at 215, 254, and 285 nm; chemical ionization at atmospheric pressure (APCI), scanning range *m/z* 80–1000. Melting points were measured on a Fisher–Johns instrument.

8-Aroylamino-7-thioxo-1,2,3,7-tetrahydroimidazo[1,2-*c*]pyrimidines 2a–c. A suspension of compound **1a–c** (2 mmol) and triethyl orthoformate (15 ml) was boiled for 3 h. After cooling, the solid was filtered off, washed with diethyl ether, and purified by recrystallization.

2-Aryl-7,8-dihydroimidazo[1,2-*c*][1,3]thiazolo[4,5-*e*]pyrimidines 3a–c. A. Phosphorus pentasulfide (0.49 g, 2.2 mmol) was added to a solution of one of the compounds **2a–c** (2 mmol) in anhydrous pyridine (10 ml). The mixture was boiled with stirring for 5 h, cooled, water (40–50 ml) was added, the precipitated solid was filtered off, washed with water, and purified by recrystallization.

B. A mixture of one of the compounds **2a–c** (2 mmol) and polyphosphoric acid (10 ml) was heated for 5 h on an oil bath at 160°C, then cooled, the mixture was poured onto ice, the precipitated solid filtered off, washed with 5% aqueous $NaHCO_3$ solution, and purified by recrystallization.

X-ray Structural Investigation of a monocrystal of compound **3c** (0.13×0.15×0.49 mm) was carried out at room temperature on a Bruker Apex II automatic CCD diffractometer (Mo*K*α radiation, $\lambda = 0.71073$ Å, $\theta_{max} = 26.3^{o}$, $-8 \le h \le 8$, $-12 \le k \le 12$, $-13 \le l \le 13$). In total 8762 reflections were collected (1808 independent reflections, $R_{int} = 0.003$). Crystals of compound **3c** were triclinic, $a = 7.0498(9)$, $b = 10.393(1)$, $c = 11.075(1)$ Å, $\alpha = 102.349(4)^{o}$, $\beta = 96.043(4)^{o}$, $\gamma = 91.436(4)^{o}$, $V = 787.3(2)$ Å^3, $M = 334.83$, $Z = 2$, $d_{calc} = 1.41$ g/cm^3, $\mu = 3.82$ cm^{-1}, $F(000) = 348$, space group $P\bar{1}$ (N 2). The structure was solved by the direct method and refined by the least squares method in a full matrix anisotropic approximation using the CRYSTALS set of programs [19]. In the refinement 1808 reflections with $I > 3\sigma(I)$ were used. All the hydrogen atoms were made apparent by an electron density difference synthesis and were included in the refinement with fixed positions and thermal parameters (with the exception of atom H-1, which was refined isotropically). The Chebyshev weighting factor [20] was used in the refinement with five parameters: 2.10, 2.19, 1.97, 0.49, and 0.35. The final values of the divergence factor $R = 0.039$ and $R_w = 0.047$, GooF 0.908. The residual electron density from the Fourier difference series was 0.30 and –0.38 e/Å^3. A complete set of the X-ray structural data for compound **3c** has been deposited in the Cambridge Structural Database (deposit CCDC 768487).

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