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SYNTHESIS OF CONDENSED DERIVATIVES OF 2-SUBSTITUTED THIENO[2,3-*d*]PYRIMIDIN-4-ONES

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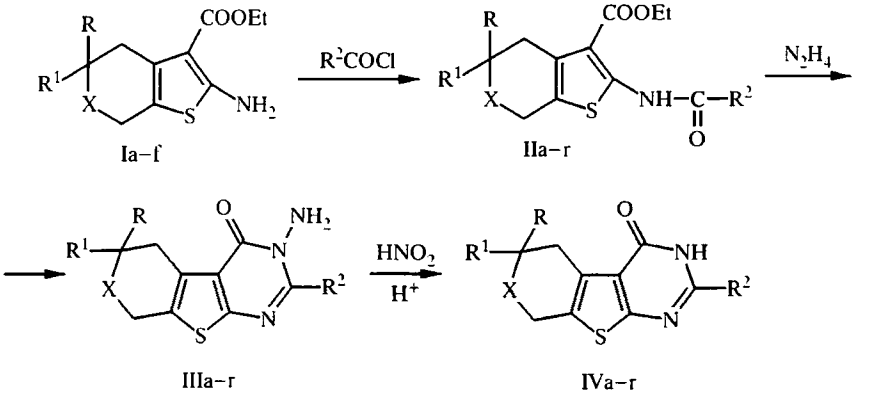
A preparative method of synthesis of 2-substituted thieno[2,3-d]pyrimidin-4-ones involving deamination of the corresponding 3-amino derivatives by sodium nitrite in acidic medium is proposed. A possible reaction mechanism is considered.

2-Substituted thieno[2,3-*d*]pyrimidines exhibit a wide spectrum of biological activity [1-3]. Therefore the synthesis of similar compounds is of great interest. Various methods of preparing them have been reported [3-5]. However, these methods are somewhat specific and do not always give the desired product in high yield.

We synthesized condensed derivatives of 2-substituted 4-oxo-5,6-dihydro[2,3-*d*]pyrimidines IVa-r in quantitative yields starting with 2-amino-3-ethoxycarbonylthiophenes Ia-f, acylating them to give IIa-r [6, 8], condensing IIa-r with hydrazine hydrate, and deaminating the obtained 3-aminopyrimidines IIIa-r. The products IVa-e were obtained for the first time. Their properties are listed in Table 1. Compounds IVf-r are identical to those described previously [6-9].



Ia, II-IVa-h X = O, R = R^1 = Me, a R^2 = C_3H_7-*i*, b R^2 = C_4H_9-*i*, c R^2 = C_9H_{19}, d R^2 = *cyclo*-C_6H_{11}, e R^2 = Ph, f R^2 = C_3H_7, g R^2 = C_4H_9, h R^2 = C_5H_{11}; Ib, II-IVi X = O, R = H, R^1 = Me, R^2 = C_3H_7; Ic, II-IVj-l X = S, R = R^1 = Me, j R^2 = C_3H_7, k R^2 = C_4H_9, l R^2 = C_5H_{11}; Id, II-IVm X = NMe, R = R^1 = Me, R^2 = C_4H_9; Ie, II-IVn-q X = CH_2, R = R^1 = H, n R^2 = C_3H_7, o R^2 = C_4H_9, p R^2 = C_5H_{11}, q R^2 = C_4H_9-*i*; If, II-IVr X = CH_2, R = H, R^1 = Me, R^2 = C_5H_{11}

The mentioned route is new and simple preparative method for synthesis of the compounds of type IV. It enables various substituents to be introduced into the 2-position of the pyrimidine ring.

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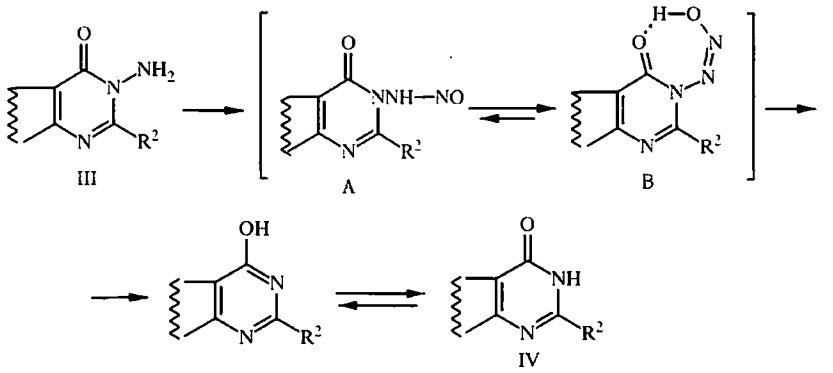
TABLE 1. Characteristics of the Synthesized Compounds IVa-e

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	R_f*	PMR spectrum, δ, ppm				
		C	H	N	S			NH (1H, s)	R,R¹ (6H, s)	CH_2 (2H, t)	OCH_2 (2H, t)	R^2
IVa	$C_{14}H_{18}N_2O_2S$	60.61 / 60.41	6.48 / 6.51	10.19 / 10.06	11.40 / 11.51	250	0.46	12.60	1.32	3.15	4.73	1.10 (6H, t, $2CH_3$); 3.65 (1H, q, CH)
IVb	$C_{15}H_{20}N_2O_2S$	61.60 / 61.64	6.87 / 6.91	9.60 / 9.58	11.00 / 10.96	245	0.53	12.60	1.33	3.13	4.74	1.00 (6H, d, $2CH_3$); 2.50 (2H, q, CH_2) 2.20 (1H, m, CH)
IVc	$C_{20}H_{30}N_2O_2S$	66.34 / 66.29	8.30 / 8.34	7.81 / 7.73	8.80 / 8.84	200-202	0.60	12.62	1.31	3.20	4.80	0.85 (3H, t, CH_3) 1.20-2.40 (16H, m, $8CH_2$)
IVd	$C_{17}H_{22}N_2O_2S$	64.20 / 64.14	6.87 / 6.97	8.89 / 8.80	10.10 / 10.07	315	0.56	12.40	1.32	3.15	4.75	1.86 (10H, m, $5CH_2$) 2.20 (1H, m, CH)
IVe	$C_{17}H_{16}N_2O_2S$	65.41 / 65.37	5.10 / 5.16	8.91 / 8.97	10.36 / 10.26	332	0.60	12.45	1.33	3.14	4.80	7.85 (5H, s, C_6H_5)

* Chloroform–ethyl acetate–heptane, 1:1:2.

An intermediate A is apparently produced on the first stage during the deamination of amines III at room temperature by aqueous solution of sodium nitrite in the presence of acetic acid. The NH hydrogen atom in the intermediate A migrates to the oxygen atom with simultaneous elimination of N_2O. The proposed reaction mechanism possibly includes a concerted process passing through the cyclic transition state B:



The analogous deamination of two series of 1-amino-9-alkylhypoxanthines was reported [10]. A side product from the reaction of aliphatic hydrazides is the primary amide [11].

The structures of III-IVa-r were confirmed by PMR and IR spectra. Thus, the PMR spectra of these amines contain singlets at 4.80-4.90 ppm, characteristic of the NH_2 moiety. These singlets are absent in the spectra of the deamination products IVa-r, which contain a signal for the NH moiety at weak field (12.20-12.50 ppm), characteristic of cyclic amides. The IR spectra of IIIa-r contain bands assigned to NH_2 stretching vibrations (3130-3380 cm^{-1}) whereas those of IVa-r have absorption bands in the region of 3240 cm^{-1}, characteristic of NH amide moiety.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrometer in vaseline oil. PMR spectra were obtained on a Varian T-60 instrument with TMS as internal standard. The purity of the products was monitored by TLC on Silufol UV-254 plates using chloroform–ethyl acetate–heptane (1:1:2) as eluent and were visualized using iodine vapor. The R_f values of IId, IIId, and IVa-e were also determined using this solvent system. The starting amino esters Ia-f were synthesized by the literature method [13].

3-Carbethoxy-2-(N-cyclohexylcarbamoyl)-5,5-dimethyl-4,5-dihydro-7H-thieno[2,3-*c*]-pyran (IId). Solution of compound Ia [11] (0.01 mol) in dry dioxane (30 ml) was treated with cyclohexanecarboxylic acid chloride (1.46 g, 0.01 mol) The mixture was boiled for 3 h, cooled, and poured into cold water (200 ml). The crystals of the product IId were filtered off, washed with water and alcohol, and dried. Yield 3.2 g (89.6%); mp 102-105°C. R_f 0.65. IR spectrum: 3230 (NH), 1680 (CO), 1665 cm^{-1}. PMR spectrum: 11.20 (1H, s, NH); 4.60 (2H, t, OCH_2); 4.30 (2H, q, $O\underline{CH_2}CH_3$); 2.70 (2H, t, CH_2); 2.40-1.50 (11H, m, *cyclo*-C_6H_{11}); 1.40 (3H, t, $OCH_2\underline{CH_3}$); 1.25 ppm (6H, s, $2CH_3$). Found, %: C 62.12; H 7.46; N 4.0; S 8.70. $C_{17}H_{22}N_2O_2S$. Calculated, %: C 62.46; H 7.39; N 3.83; S 8.76.

2-Substituted 3-Amino-6,6-dimethyl-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-ones (IIId,e). Mixture of compound IId or IIe [12] (0.01 mol) and hydrazine hydrate (20 ml) in ethanol (4 ml) was boiled for 8 h and then cooled. The resulting crystals of IIId or IIIe were successively filtered off and washed with water and alcohol.

3-Amino-2-cyclohexyl-6,6-dimethyl-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (IIId). Yield 2.8 g (85.3%); mp 199-200°C. R_f 0.58. IR spectrum: 3320, 3180 (NH_2); 1665 cm^{-1} (CO). PMR spectrum: 5.50 (2H, s, NH_2); 4.80 (2H, t, CH_2); 2.80 (2H, t CH_2); 2.60-1.30 (11H, m, *cyclo*-C_6H_{11}); 1.32 ppm (6H, s, $2CH_3$). Found, %: C 61.36; H 7.10; N 12.41; S 9.70. $C_{17}H_{23}N_3O_2S$. Calculated, %: C 61.26; H 6.96; N 12.61; S 9.62.

3-Amino-6,6-dimethyl-2-phenyl-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (IIIe). Yield 2.7 g (83.1%); mp 213-215°C. R_f 0.52 (chloroform–ethyl acetate–hexane, 1:1:1). IR spectrum: 3325, 3185 (NH_2); 1660 cm^{-1} (CO). PMR spectrum: 8.20-7.30 (5H, m, Ph); 5.45 (2H, s, NH_2); 4.80 (2H, t, CH_2); 2.80 (2H, t, CH_2); 1.33 ppm (6H, s, $2CH_3$). Found, %: C 62.40; H 8.31; N 12.65; S 9.81. $C_{17}H_{17}N_3O_2S$. Calculated, %: C 62.38; H 8.38; N 12.85; S 9.80. The previously known compounds IIIa-c,f-r were synthesized analogously and had properties consistent with the literature data [8, 9].

Synthesis of 2-Substituted 6,6-Dimethyl-4-oxo-5,6-dihydro-8H-pyrano(4',3':4,5)thieno[2,3-*d*]-pyrimidines (IVa-e). General method. Solution of compound III (0.01 mol) in glacial acetic acid (40 ml) was treated dropwise with stirring at room temperature with solution of sodium nitrite (1.46 g, 0.02 mol) in water (3 ml). The resulting mixture was held for 16 h at room temperature. The resulting crystals were filtered off. The filtrate was diluted with cold water. The resulting crystals were filtered off, combined with those obtained from the first filtration, washed with water, and recrystallized from ethanol. Yields of compound IV are quantitative. The properties of compounds IVa-e are given in Table 1.

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