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SYNTHESIS OF 1,2,3-THIADIAZOLO[5,4-*d*]PYRIMIDINES

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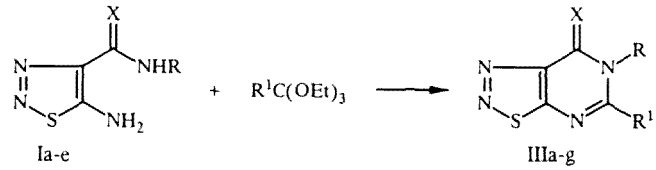
We have obtained a series of 1,2,3-thiadiazolo[5,4-d]pyrimidines by condensation of 5-(R-amino)-substituted-1,2,3-thiadiazole-4-N-R-(thio)carboxamides with ortho esters.

1,2,3-Thiadiazoles condensed with other heterocyclic systems are a little-studied class of organic compounds. Of special interest as potentially biologically active compounds are 1,2,3-thiadiazolo[5,4-*d*]pyrimidines, which are structural analogs of natural purine systems. However, no general convenient procedure has yet been devised for obtaining the indicated compounds. The few examples of the synthesis of thiadiazolopyrimidines [1] are reduced either to a multistep annelation of the thiadiazole ring to a pyrimidine ring, or to condensation of 5-amino-4-ethoxycarbonyl-1,2,3-thiadiazole with acetates of formamidine and acetamidine, occurring in low yields. There are no data in the literature on the reaction of 5-amino-1,2,3-thiadiazole-4-carboxamides with ortho esters, while this method is a convenient preparative method for construction of a pyrimidine system and was used earlier for obtaining imidazo[5,4-*d*]pyrimidines [2].

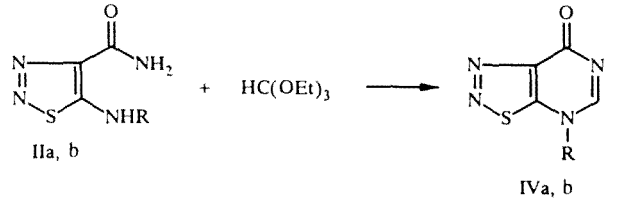
The goal of this work was to develop a general method for synthesis of thiadiazolopyrimidine systems based on condensation with ortho esters of 5-amino-1,2,3-thiadiazole-4-N-R-(thio)carboxamides (I), and also 5-R-amino-1,2,3-thiadiazole-4-carboxamides (II), obtained according to previously described procedures [3-6].



I, III a—d X = O, R^1 = H, a R = H, b R = Me, c R = CH_2Ph, d R = cyclo-C_6H_{11};
I, III e X = S, R = R^1 = H; III f,g X = O, R^1 = Me, f R = Me, g R = CH_2Ph

We have established that on heating the substituted carboxamides Ia-d with excess ethylorthoformate at 130-140°C, the corresponding crystalline 1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-ones (IIIa-d) are formed in 20-80% yields, the structure of which are confirmed by PMR and IR spectra. In the PMR spectra of compounds IIIa-d, we detected a signal in the 8.5-9.5 ppm region, characteristic for protons of the pyrimidine ring. The melting point of product IIIa obtained by the indicated method matches the value given in the literature [1]. Substitution of the carboxamide group by a thiocarboxamide group does not change the orientation of the reaction: on reaction of 5-amino-1,2,3-thiadiazole-4-thiocarboxamide Ie with ethylorthoformate, the compound 1,2,3-thiadiazolo[5,4-*d*]pyrimidine-4-thione (IIIe) is formed.

In analogous reactions of compounds Ib,c with ethylorthoacetate, we obtained 6-methyl-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-ones (IIIf,g).



II, IV a R = CH_2Ph, b R = Pr-*i*

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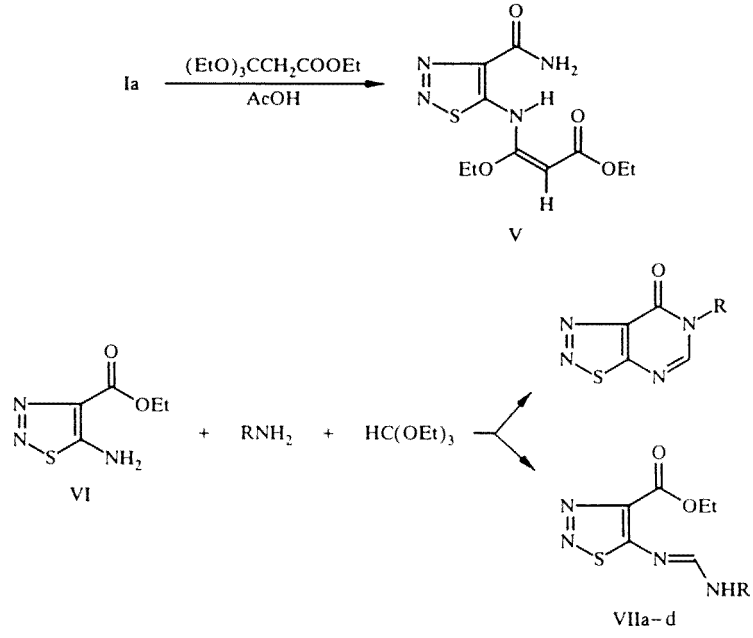
The reaction of ethylorthoformate with 5-alkylamino-1,2,3-thiadazole-4-carboxamides IIa,b under the same conditions led to formation of 7-alkyl-substituted 1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-ones (IVa,b). We should note that 5-acetylamino-1,2,3-thiadiazole-4-carboxamide does not react with ortho esters. This is probably connected with the lower nucleophilicity of the nitrogen atom of the acetamide group compared with the amino functional group.

In contrast to ortho esters which are not functionally substituted, ethylorthoethoxycarbonylacetate does not form a bicyclic product with amide Ia; in this case, we obtain the enamine V in 4% yield.



VII a R = C_6H_4OMe-o, b R = C_6H_4OMe-m, c R = C_6H_4OMe-*p*,
d R = 4-carbethoxy-1,2,3-thia-5-diazolyl

With the goal of developing a more general procedure for constructing a thiadiazolopyrimidine system, we also tested another variant of condensation with participation of three components. We showed that on heating the more accessible 5-amino-4-ethoxycarbonyl-1,2,3-thiadiazole (VI) with an equivalent amount of benzylamine and ethylorthoformate in benzonitrile, a product is formed in 36% yield which has the same characteristics as the previously obtained sample of compound IIIc. Its analog IIIh is obtained similarly from 1-methyl-3-phenylpropylamine. However, when using less nucleophilic aromatic amines in the considered reaction, we isolated intermediate products: the formamidines (VIIa-d).

Thus we have developed effective and convenient preparative syntheses of 1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-ones (thiones).

EXPERIMENTAL

The PMR spectra were obtained on a Tesla-567A spectrometer (80 Hz and 100 MHz) in DMSO-D_6, internal standard TMS. The IR spectra were recorded on a UR-20 spectrometer in KBr pellets. The course of the reaction and the purity of the synthesized compounds were monitored using TLC on DC-Plastikfolien Kieselgel 60 F 254 plates in the system chloroform—ethanol, 9:1. The melting points were uncorrected.

The compounds Ia-e,f and VI were obtained by the familiar method in [3-6].

5-Benzylamino-4-carbamoyl-1,2,3-thiadiazole (IIa) was obtained by the procedure in [3]. Yield, 64%. mp, 134-135°C (from heptane). PMR spectrum: 9.1 (1H, t, J = 5.7 Hz, N<u>H</u>R), 7.9 (1H, broad s, H_{NH2}), 7.4 (6H, s, $5H_{Ph}$,H_{NH2}), 4.5 ppm (2H, d, J = 5.7 Hz, CH_2). Found, %: C 51.43, H 4.81, N 24.20, S 13.65. $C_{10}H_{10}N_4SO$. Calculated, %: C 51.27, H 4.30, N 23.91, S 13.69.

5-Isopropylamino-4-carbamoyl-1,2,3-thiadiazole (IIb) was obtained by the procedure in [3]. Yield, 42%. mp 132-134°C (from heptane). PMR spectrum: 8.4 (1H, d, J = 8.0 Hz, N<u>H</u>R), 7.9 (1H, broad s, H_{NH2}), 7.5 (1H, broad s, N_{NH2}),

3.3 (1H, m, CH), 1.3 ppm (6H, d, J = 6.2 Hz, $2CH_3$). Found, %: C 38.49, H 4.82, N 30.63, S 17.35. $C_6H_{10}N_4SO$. Calculated, %: C 38.70, H 5.41, N 30.08, S 17.22.

Condensation of 5-R-Amino-1,2,3-thiadiazole-4-R-(thio)carboxamides with Ortho Esters. A. A suspension of 1 g 5-R-amino-1,2,3-thiadiazole-4-R-(thio)carboxamide I or II in 10 ml ortho ester was stirred for 5-6 h at 130°C. The precipitate of product III formed on cooling was filtered off, washed with ether, and crystallized.

Condensation of 5-Amino-4-ethoxycarbonyl-1,2,3-thiadiazole with Amines and Ethylorthoformate. B. A mixture of 5.8 mmoles thiadiazole VI, 5.8 mmoles of the corresponding amine and 0.96 ml (5.8 mmoles) ethylorthoformate was held in 7 ml benzonitrile at 130°C for 5 h. The product III or VII was precipitated from 70 ml heptane and crystallized.

5-Methyl-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-one (IIIb) was obtained by method A. Yield, 70%. mp 187-188°C (from acetonitrile). IR spectrum: 1700 cm^{-1} (C=O). PMR spectrum: 8.8 (1H, s, CH), 3.59 ppm (3H, s, CH_3). Found, %: C 36.03, H 2.21, N 33.40, S 19.23. $C_5H_4N_4SO$. Calculated, %: C 35.70, H 2.40, N 33.31, S 19.07.

5-Benzyl-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-one (IIIc) was obtained by methods A and B. Yield: 80% by method A, 34% by method B. mp 147-148°C (from acetonitrile). IR spectrum: 1700 cm^{-1} (C=O). PMR spectrum: 9.0 (1H, s, H_{Het}), 7.4 (5H, s, H_{Ph}), 5.3 ppm (2H, s, CH_2). Found, %: C 54.36, H 3.33, N 22.98, S 13.43. $C_{11}H_8N_4SO$. Calculated, %: C 54.08, H 3.31, N 22.94, S 13.13.

5-Cyclohexyl-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-one (IIId) was obtained by method A. Yield, 34%. mp 219°C (from acetonitrile). IR spectrum: 1700 cm^{-1} (C=O). PMR spectrum: 8.8 (1H, s, H_{Het}), 4.7 (1H, m, $CH_{cyclohexyl}$), 2.1-1.2 ppm (10H, m, $5CH_2$). Found, %: C 50.63, H 4.98, N 23.67, S 13.86. $C_{10}H_{12}N_4SO$. Calculated, %: C 50.83, H 5.12, N 23.71, S 13.57.

1,2,3-Thiadiazolo[5,4-*d*]pyrimidine-4-thione (IIIe) was obtained by method A, but with stirring for 0.5 h. Yield, 28%. mp 236-239°C (decomposes, from ethanol). PMR spectrum: 14.5 (1H, broad s, NH), 8.5 ppm (1H, s, CH). Found, %: C 31.43, H 0.98, N 36.47, S 20.65. $C_4H_2N_4SO$. Calculated, %: C 31.1, H 1.3, N 36.3, S 20.8.

5,6-Dimethyl-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-one (IIIf) was obtained by method A. Yield, 30%. mp 168-169°C (from acetonitrile). PMR spectrum: 3.6 (3H, s, NCH_3), 2.7 ppm (3H, s, Me). Found, %: C 39.43, H 3.2, N 30.89, S 17.65. $C_6H_6N_4SO$. Calculated, %: C 39.55, H 3.32, N 30.75, S 17.60.

5-Benzyl-6-methyl-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-one (IIIg) was obtained by method A. Yield, 20%. mp 129-130°C (from acetonitrile). IR spectrum: 1700 cm^{-1} (C=O). PMR spectrum: 7.3 (5H, s, H_{Ph}), 5.5 (2H, s, CH_2), 2.6 ppm (3H, s, Me). Found, %: C 55.43, H 3.88, N 21.60, S 21.66. $C_{12}H_{10}N_4SO$. Calculated, %: C 55.80, H 3.90, N 21.69, S 12.41.

5-(1-Methyl-3-phenylpropyl)-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-one (IIIh) was obtained by method B. The product was precipitated in the form of an oil, which crystallized on trituration in ethanol. Yield, 32%. mp 107°C (from ethanol). IR spectrum: 1700 cm^{-1} (C=O). PMR spectrum: 8.8 (1H, s, H_{Het}), 7.2 (5H, s, H_{Ph}), 5.0 (1H, q.t, $^3J_{CH-CH3}$ = 7.1, $^3J_{CH-CH2}$ = 7.1 Hz, CH), 2.8-2.0 (4H, m, CH_2—CH_2), 1.5 ppm (3H, d, J = 7.1 Hz, CH_3). Found, %: C 58.77, H 4.66, N 19.76, S 11.13. $C_{14}H_{14}N_4SO$. Calculated, %: C 58.72, H 4.93, N 19.57, S 11.20.

7-Benzyl-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-one (IVa) was obtained by method A. Yield, 14%. mp 182°C (from acetonitrile). IR spectrum: 1645 cm^{-1} (C=O). PMR spectrum: 8.9 (1H, s, H_{Het}), 7.4 (5H, s, H_{Ph}), 5.5 ppm (2H, s, CH_2). Found, %: C 54.16, H 3.44, N 22.91, S 12.99. $C_{11}H_8N_4SO$. Calculated, %: C 54.09, H 3.30, N 22.94, S 13.13.

7-Isopropyl-1,2,3-thiadiazolo[5,4-*d*]pyrimidin-4-one (IVb) was obtained by method A. Yield, 19%. mp 210°C (from acetonitrile). IR spectrum: 1645 cm^{-1} (C=O). PMR spectrum: 8.8 (1H, s, H_{Het}), 4.6 (1H, septet, J = 6.7 Hz, CH_2), 1.6 ppm (6H, d, J = 6.7 Hz, $2CH_3$). Found, %: C 42.94, H 4.27, N 28.43, S 16.66. $C_7H_8N_4SO$. Calculated, %: C 42.85, H 4.11, N 28.55, S 16.34.

5-(1-Ethoxy-2-ethoxycarbonylvinyl)amino-4-carbamolyl-1,2,3-thiadiazole (V). A mixture of 2 g (13.9 mmoles) amide Ia, 1.4 ml (13.9 mmoles) ethylorthoethoxycarbonylacetate and 0.08 ml (1.39 mmoles) glacial acetic acid was boiled in 20 ml acetonitrile for 24 h. The reaction mixture was cooled down to 0°C, the precipitating product was filtered off and crystallized from acetonitrile. Yield, 4%. mp 178-179°C. IR spectrum: 1650 ($C=O_{ester}$), 1620 cm^{-1} ($C=O_{amide}$). PMR spectrum: 12.8 (1H, s, NH), 8.1 (1H, broad s, H_{NH2}), 7.7 (1H, broad s, H_{NH2}), 4.7 (1H, s, CH), 4.3 (2H, q, J = 7.0 Hz, OCH_2), 4.16 (2H, q, J = 7.0 Hz, OCH_2), 1.5 (3H, t, J = 7.0 Hz, CH_3), 1.3 ppm (3H, t, J = 7.0 Hz, CH_3). Found, %: C 38.49, H 5.2, N 30.33, S 17.35. $C_{16}H_{10}N_4SO$. Calculated, %: C 38.70, H 5.41, N 30.08, S 17.22.

N^2-(4-Ethoxycarbonyl-1,2,3-thiadiazolo-5-yl)-N^2-(2-methoxyphenyl)formamidine (VIIa) was obtained by method B. Yield, 38%. mp 172-174°C. IR spectrum: 1670 cm^{-1} (C=O). PMR spectrum: 11.3 (1H, broad s, NH), 8.5 (1H, d, J = 2.5 Hz, CH), 7.4-6.8 (4H, m, 2-, 3-, 5-, and 6-H_{Ar}), 4.5 (2H, q, J= 7.0 Hz, CH_2), 3.8 (3H, s, OCH_3), 1.4 ppm (3H, t, J = 7.0Hz, CH_3). Found, %: C 50.76, H 4.69, N 18.44, S 10.49. $C_{13}H_{14}N_4SO_3$. Calculated, %: C 50.97, H 4.61, N 18.29, S 10.47.

N^2-(4-Ethoxycarbonyl-1,2,3-thiadiazol-5-yl)-N^1-(3-methoxyphenyl)formamidine (VIIb) was obtained by method B. Yield, 31%. mp 174°C. IR spectrum: 1670 cm^{-1} (C=O). PMR spectrum: 11.3 (1H, broad s, NH), 8.4 (1H, broad s, CH), 7.5-7.2 (1H, m, 2-H_{Ar}), 6.9-6.7 (3H, m, 4-, 5-, and 6-H_{Ar}), 4.5 (2H, q, J = 7.0 Hz, CH_2), 3.8 (3H, s, OCH_3), 1.4 ppm (3H, t, J = 7.0 Hz, CH_3). Found, %: C 50.88, H 4.49, N 18.58, S 10.34. $C_{13}H_{14}N_4SO_3$. Calculated, %: C 50.97, H 4.61, N 18.29, S 10.47.

N^2-(4-Ethoxycarbonyl-1,2,3-thiadiazol-5-yl)-N^1-(4-methoxyphenyl)formamidine (VIIc) was obtained by method B. Yield, 45%. mp 189-190°C. IR spectrum: 1670 cm^{-1} (C=O). PMR spectrum: 11.2 (1H, broad s, NH), 8.4 (1H, d, J = 2.53 Hz, CH), 7.2 (2H, d, $^3J_{Ho\text{-}Hm}$ = 9.1 Hz, 2- and 6-H_{Ar}), 7.0 (2H, d, $^3J_{Ho\text{-}Hm}$ = 9.1 Hz, 3- and 5-H_{Ar}), 4.5 (2H, q, J = 7.0 Hz, CH_2), 3.8 (3H, s, OCH_3), 1.4 ppm (3H, t, J = 7.0 Hz, CH_2). Found, %: C 50.88, H 4.49, N 18.58, S 10.34. $C_{13}H_{14}N_4SO_3$. Calculated, %: C 50.97, H 4.61, N 18.29, S 10.47.

N,N′-bis(4-Ethoxycarbonyl-1,2,3-thiadiazol-5-yl)formamidine (VIId) was obtained by method A. Yield, 10%. mp 163°C (from ethanol). PMR spectrum (60°C): 11.9 (1H, broad s, NH), 8.5 (1H, broad s, CH), 4.5 (2H, q, J = 8.0 Hz, CH_2), 4.4 (2H, q, J = 8.0 Hz, CH_2), 1.4 (3H, t, J = 8.0 Hz, CH_3), 1.3 ppm (3H, t, J = 8.0 Hz, CH_3). Found, %: C 37.48, H 3.49, N 23.78, S 18.34. $C_{11}H_{12}N_6S_2O_4$. Calculated, %: C 37.07, H 3.39, N 23.58, S 17.99.

REFERENCES

1. W. E. Hymans, J. Heterocycl. Chem., **13**, 1141 (1976).
2. V. V. Mezheritskii, E. P. Olekhnovich, S. M. Luk'yanov, and G. N. Dorofeenko, Ortho Esters in Organic Synthesis [in Russian], Izdat. Rost. Univ., Rostov-na-Donu (1976), p. 149.
3. Yu. Yu. Morzherin, E. V. Tarasov, and V. A. Bakulev, Khim. Geterotsikl. Soedin., No. 4, 548 (1994).
4. V. A. Bakulev, A. T. Lebedev, E. F. Dankova, V. S. Mokrushin, and V. S. Petrosyan, Tetrahedron Lett., **45**, 7329 (1989).
5. Yu. M. Shafran, V. A. Bakulev, V. S. Mokrushin, and Z. V. Pushkareva, Khim. Geterotsikl. Soedin., No. 12, 1696 (1982).
6. M. Yu. Kolobov, V. A. Bakulev, and V. S. Mokrushin, Zh. Org. Khim., **23**, 1120 (1987).