Chemistry of Heterocyclic Compounds, Vol. 45, No. 7, 2009

SYNTHESIS OF THIAZOLO[3,2-*a*]PYRIMIDINES BASED ON 4-ARYL-SUBSTITUTED 3,4-DIHYDRO-PYRIMIDINE(1H)-2-THIONES AND THE CRYSTAL STRUCTURE OF ETHYL 5-(2,4-DIMETHOXYPHENYL)-7-METHYL-3-OXO-3,5-DIHYDRO-2H-THIAZOLO-[3,2-*a*]PYRIMIDINE-6-CARBOXYLATE

I. V. Kulakov[1]*, O. A. Nurkenov[1], D. M. Turdybekov[2], G. M. Issabaeva[1], A. S. Mahmutova[2], and K. M. Turdybekov[2]

Thiazolo[3,2-a]pyrimidines were obtained in good yield by the reaction of 4-aryl-substituted 3,4-dihydropyrimidine(1H)-2-thiones and methyl chloroacetate in boiling toluene. Their structures were shown by ^{1}H NMR spectroscopy and X-ray crystallography.

Keywords: 3,4-dihydropyrimidine(1H)-2-thiones, 3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidine, methyl chloroacetate, intramolecular heterocyclization, X-ray crystallography, ^{1}H NMR spectroscopy.

Recently there has been a considerable growth in the number of publications on the chemistry of 4-aryl-3,4-dihydropyrimidin-2-ones and 4-aryl-3,4-dihydropyrimidine-2-thiones obtained by three-component condensation in the Biginelli reaction is associated with the displaying by these readily available compounds a wide range of pharmacological activities – analgesic, antibacterial, antihypertensive, etc. [1-3]. The attention of synthetic chemists was drawn to the presence in 4-aryl-3,4-dihydropyrimidine-2-thiones of several reactive nucleophilic centers allowing for a variety of mono- and dialkylation, acylation [4-6], and also the very prospective cyclization reaction. For example, the conversion of 4-phenyl-3,4-dihydropyrimidine(1H)-2-thione into 3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidine by boiling it in DMF with chloroacetic acid has been described [7]. Attempts to carry out analogous cyclizations with 4-methoxy- and 2,4-dimethoxyphenyl-substituted 3,4-dihydropyrimidine(1H)-2-thiones gave rise to considerable amounts brightly colored by-products, difficult to separate from the desired product.

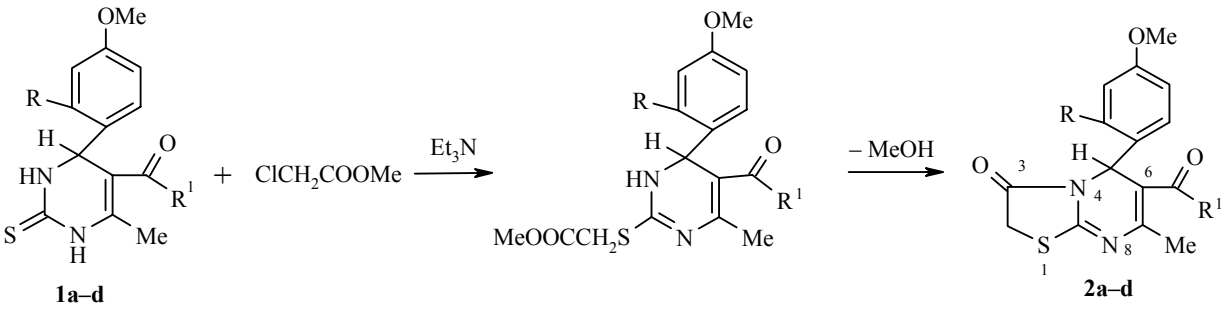
* To whom correspondence should be addressed, e-mail: kulakov_iv@mail.ru.

[1]Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, Karaganda 100008, Kazakhstan.
[2]Research and Production Center "Phytochemistry", Ministry of Education and Science of the Republic of Kazakhstan, Karaganda 100009, Kazakhstan.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No.7, 1075-1079, July, 2009. Original article submitted July 7, 2008.

We have developed a new preparatively more simple method, based on 4-aryl-substituted 3,4-dihydropyrimidine(1H)-2-thiones **1a-d,** to obtain 3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidines which involves the boiling of solutions of compounds **1a-d** in toluene with a slight excess of methyl chloroacetate in the presence of triethylamine. The starting materials **1a-d** were obtained by a three-component condensation of the corresponding aldehydes, thiourea, and ethyl acetoacetate (compounds **1a** and **1b**) or acetylacetone (compounds **1c** and **1d**) by boiling in DMF as described elsewhere [5]. The structures of compounds **1a-d** were confirmed by ^{1}H NMR spectroscopy and other physical characteristics coincided with literature data [8, 9].

In each of the examples studied the formation of products of S- or N-alkylation was possible, but in all cases only the desired products of cyclization **2a-d** were isolated in 84-90% yield.



1,2 a R = H, R^1 = OEt; **b** R = OMe, R^1 = OEt; **c** R = H, R^1 = Me; **d** R = OMe, R^1 = Me

The formation of compounds **2a-d** was confirmed by the absence of amino group absorptions in the IR spectra, and in the ^{1}H NMR spectra absence of the signals of the COOMe and the N(3) proton which were present in the spectra of the starting materials and in the products of their N(1) monoalkylation (doublet in the 9.2 ppm region). The signals of the protons of the CH_2 unit in the thiazolidine ring appear as a doublet of doublets with J = 17.7 Hz.

With the objective of determining the spatial structure of the synthesized bicyclic thiazolo-[3,2-*a*]pyrimidines we carried out an X-ray crystallographic investigation of compound **2b**.

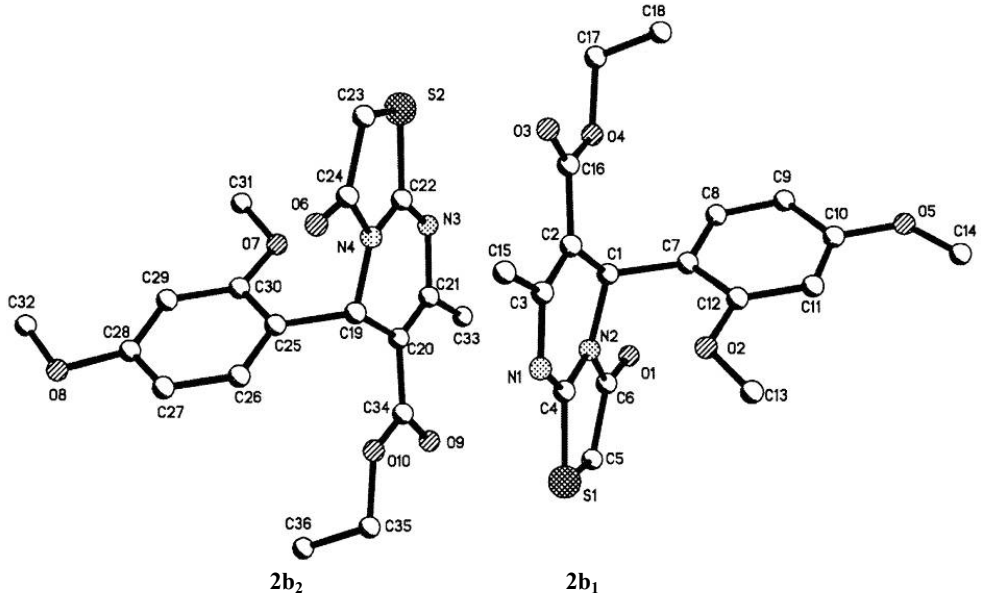


Fig. 1. The Positions of the Independent Molecules **2b$_1$** and **2b$_2$** in the Unit Cell.

The unit cell contained two geometrically independent molecules **2b$_1$** and **2b$_2$** (Figure 1). The bond lengths and valence angles were close to standard values [10]. The thiazolidine ring in each molecule is almost planar (deviation ± 0.03Å) with the sulfur atoms 0.12 Å from the planes of the remaining atoms, in which atoms O(1) and O(6) of the carbonyl groups also lie. The pyrimidine rings have a *flattened sofa* conformation ($\Delta C(1)_s$ = 5.34 and $\Delta C(19)_s$ = 5.48 Å) with atoms C(1) and C(19) out of their planes by 0.24 and 0.19 Å respectively; this ring may take a distorted *boat* conformation as in 5-nitro-4-(2-nitrophenyl)-6-phenyl-3,4-dihydro-(1H)-pyrimidin-2-one [11].

The dimethoxyphenyl substituents are oriented axially to the basic skeleton of the molecules (torsion angles C(2)C(3)C(7)C(8) and C(20)C(19)C(25)C(26) are equal to -109.33° and 110.84° respectively). In both molecules the methoxy groups lie in the planes of the benzene ring, probably because of repulsion of the oxygen atom and the nitrogen atom of the pyrimidine ring (the distances between N(1) and O(2) and between N(3) and O(7) are 3.02 and 2.98 Å respectively). The COOEt groups in both molecules are orientated equatorially (torsional angles C(1)C(2)C(16)O(4) and C(19)C(20)C(34)O(10) 9.44° and -5.33° respectively).

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded with a Bruker DRX500 (500 MHz) instrument and IR spectra of KBr tablets were recorded with an AVATAR-320 Fourier spectrometer. Course of reactions and purity of products were monitored by TLC on Sorbfil plates.

X-ray Crystallography. Lattice parameters and intensities of 3712 independent reflexions for compound **2b** were measured at 20°C on a BrukerP4 automatic four-circle diffractometer with a graphite monochromator and MoKα radiation (θ/2θ scanning, 2θ < 52°). Crystals were rhombic (ethanol), a = 9.495, b = 10.330, c = 11.612, V = 926.1(8) Å^3, d_{calc} = 1.350 g/cm^3, Z = 1 ($C_{36}H_{40}N_4O_{10}S_2$). Space group P-1.

In the calculation 3046 reflexions with $I > 2\sigma(I)$ were used. The structure was solved by direct methods using the program Sir-2002 [12] and refined by full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms. H atoms were found geometrically and fixed by the riding approximation. The final divergence factors were R = 0.0482 and wR_2 = 0.1369. Refinement of the geometry was carried out with the SHELXL-97 program [13]. Structural data for compound **2b** have been deposited in the Cambridge Structural Data Bank (CCDC 692504).

Ethyl 5-(4-Methoxyphenyl)-7-methyl-3-oxo-3,5-dihydro-2H-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (2). A mixture of 4-(4-methoxyphenyl)-3,4-dihydropyrimindine(1H)-2-thione (**1a**) (0.80 g, 2.6 mmol), methyl chloroacetate (0.304 g, 2.8 mmol), and triethylamine (0.9 g, 9.0 mmol) was boiled for 4 h in absolute toluene (10 ml). The crystals of triethylamine hydrochloride were filtered off and washed with a small amount of benzene which was added to the filtrate which was then evaporated. The residue was crystallized from hexane to give compound **2a** (0.81 g, 90%), which, after recrystallization three times from ethanol, consisted of light-orange transparent crystals; mp 126-127°C. IR spectrum, ν, cm^{-1}: 1736 (C=O); 1700 (C=O); 1544 (C=N). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.11 (3H, t, J = 7.1, $CH_2C\underline{H}_3$); 2.33 (3H, s, CH_3); 3.71 (3H, s, OCH_3); 4.01 (2H, q, J = 7.1, $C\underline{H}_2CH_3$); 4.10 (2H, dd, $J_1 = J_2$ = 17.7, SCH_2); 5.83 (1H, s, H-5); 6.88 and 7.16 (4H, d, J = 8.6, H arom). Found, %: C 59.17; H 5.56; N 8.32. $C_{17}H_{18}N_2O_4S$. Calculated, %: C 58.94; H 5.24; N 8.09.

Ethyl 5-(2,4-Dimethoxyphenyl)-7-methyl-3-oxo-3.5-dihydro-2H-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (2b) was obtained analogously to ester **2a** from 4-(2,4-dimethoxyphenyl)-3,4-dihydropyrimidine(1H)-2-thione (**1b**) (2.02 g, 6.0 mmol), methyl chloroacetate (0.66 g, 6.1 mmol), and triethylamine (1.23 g, 12.0 mmol). Yield 89%, after three recrystallizations from ethanol, orange-clear crystals; mp 129-130°C. IR spectrum, ν, cm^{-1}: 1730 (C=O); 1697 (C=O); 1548 (C=N). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.13 (3H, t, J = 7.1, $CH_2C\underline{H}_3$); 2.23 (3H, s, CH_3); 3.71 (3H, s, OCH_3); 3.73 (3H, s, OCH_3); 3.98 (2H, q, J = 7.1, $C\underline{H}_2CH_3$); 4.01 (2H, dd,

$J_1 = J_2$ = 17.6, SCH_2); 5.95 (1H, s, H-5); 6.46 (1H, d, J = 8.4, H arom); 6.52 (1H, s, H arom); 7.09 (1H, d, J = 8.4, H arom). Found, %: C 57.79; H 5.60; N 7.12. $C_{18}H_{20}N_2O_5S$. Calculated, %: C 57.43; H 5.36; N 7.44.

6-Acetyl-5-(4-methoxyphenyl)-7-methyl-2H-thiazolo[3,2-*a*]pyrimidin-3(5H)-one (2c) was obtained analogously to ester **2a** from 4-(2-methoxyphenyl)-3,4-dihydropyrimidine(1H)-2-thione (**1c**) (1.38 g, 5.0 mmol), methyl chloroacetate (0.55 g, 5.1 mmol), and triethylamine (1.5 g, 15.0 mmol). Yield 86%, after three recrystalizations from ethanol, dark-orange clear crystals; mp 121-122°C. IR spectrum, ν, cm^{-1}: 1732 (C=O); 1695 (C=O); 1550 (C=N). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.19 (3H, s, CH_3); 2.32 (3H, s, $C(O)CH_3$); 3.71 (3H, s, OCH_3); 4.10 (2H, dd, $J_1 = J_2$ = 17.7, SCH_2); 5.97 (1H, s, H-5); 6.88 and 7.18 (4H, d, J = 8.7, H arom). Found, %: C 61.18; H 5.51; N 8.42. $C_{16}H_{16}N_2O_3S$. Calculated, %: C 60.74; H 5.10; N 8.85.

6-Acetyl-5-(4-methoxyphenyl)-7-methyl-2H-thiazolo[3,2-*a*]pyrimidin-3(5H)-one (2d) was made analogously from 4-(2,4-dimethoxyphenyl)-3,4-dihydropyrimidine(1H)-2-thione (**1d**) (1.53 g, 5.0 mmol), methyl chloroacetate (0.55 g, 5.1 mmol), and triethylamine (1.5 g, 15.0 mmol). Yield 84%, after three recrystallizations from ethanol, dark-orange clear crystals; mp 131-133°C. IR spectrum, ν, cm^{-1}: 1742 (C=O); 1656 (C=O); 1585 (C=N). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.15 (3H, s, CH_3); 2.17 (3H, s, $C(O)CH_3$); 3.72 (3H, s, OCH_3); 3.74 (3H, s, OCH_3); 4.05 (2H, dd, $J_1 = J_2$ = 17.6, SCH_2); 6.10 (1H, s, H-5); 6.48 (1H, d, J = 8.4, H arom); 6.54 (1H, d, H arom); 7.06 (1H, d, J = 8.4, H arom). Found, %: C 59.31; H 5.56; N 8.37. $C_{17}H_{18}N_2O_4S$. Calculated, %: C 58.94; H 5.24; N 8.09.

REFERENCES

1. P.Wipf and V. Cunningham, *Tetrahedron Lett.,* **36**, 7819 (1995).
2. R. Gupta, A. K. Gupta, S. Paul, and P. L. Kachroo, *Indian J. Chem.,* **34B**, 151 (1995).
3. G. J. Grover, S. Dwonczyk, D. M. McMullin, C. S. Normadinam, and S. J. Moreland, *J. Carddiovasc. Pharmacol.,* **26**, 289 (1995).
4. M. A. Kolosov and V. D. Orlov, *Vestn. Khar'kov. Nats. Univ., Khimiya,* No. 669, issue 13 (36), 39, (2005).
5. M. A. Kolosov and V. D. Orlov, *Vestn. Khar'kov. Nats. Univ., Khimiya,* No. 731, issue 14 (37), 69, (2006).
6. M. A. Kolosov and V. D. Orlov, *Khim. Geterotsikl. Soedin.,* 292 (2005). [*Chem. Heterocycl. Comp.,* **41**, 260 (2005)].
7. M. M. Kurbanova, *Zh. Org. Khim.,* **42**, 1878 (2006).
8. M. A. Kolosov and V. D. Orlov, *Zh. Org. Farm. Khim.,* **3**, No. 2(10), 17 (2005).
9. F. Makaev, E. Styngach, M. Muntyanu, S. Pogrebnoi, Z. Rybkovskaya, and A. Barba, *Zh. Org. Khim.,* **43**, 1518 (2007).
10. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans 2,* S1 (1987).
11. T. V. Rybalova, V. F. Sedova, Yu. V. Gatilov, and O. P. Shkurko, *Zh. Struktur. Khimii,* **43**, 580 (2002).
12. M. C. Burla, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, G. Polidori, and R. Spagna, SIR2002; the program, *J. Appl. Crystallogr.,* **36**, 1103, Pt. 4 (2003).
13. G. M. Sheldrick, *SHELXL-97*. *Crystal Structure Refinement* – dos/win95/nt version + 1993-97, Release 97-2.