ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 8, pp. 1233–1234. © Pleiades Publishing, Ltd., 2008.
Published in Russian in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 8, pp. 1245–1246.

# Synthesis of a Novel Heterocyclic System—7-Methyl-1,2-dihydro-[1,2,4]triazino[3,4-*b*][1,2,4,5]tetrazine-6-thione*

**M. M. Heravi[a], M. Bakavoli[b], M. Rahimizadeh[b], G. Rajabzadeh[c], and M. Ghassemzadeh[d]**

[a] *Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran*
*e-mail: mmh1331@yahoo.com*

[b] *Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran*

[c] *Khorasan Research Institute for Food Science and Technology, Mashhad, Iran*

[d] *Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran*

Received April 29, 2006

**Abstract**—4-Amino-6-methyl-3-hydrazino-4,5-dihydro-1,2,4-triazine-5-thione reacted with triethyl orthoformate or triethyl orthoaceate in ethanol to give a novel heterocyclic system, [1,2,4]triazino[3,4-*b*][1,2,4,5]-tetrazine-6-thione.

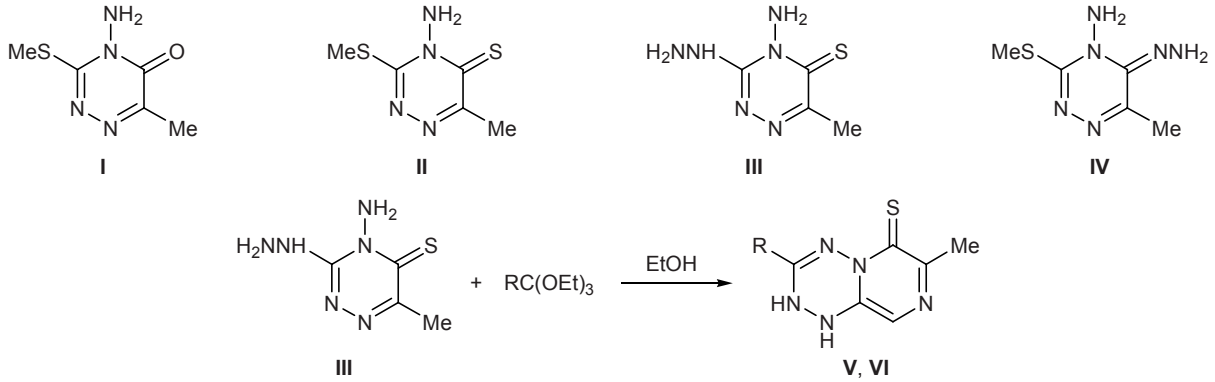
**DOI:** 10.1134/S1070428008080216

The chemistry of tetrazine and fused tetrazines has been extensively reviewed [1, 2]. Tetrazines and bicyclic compounds showed a broad spectrum of pharmacological activity [3]. Their synthesis needs conventional heterocyclization strategies [4, 5]. We are interested in heterocyclic compounds containing nitrogen and sulfur [6].

In continuation of our studies on the synthesis of heterocyclic system, in the present communication we report a facile route to 1,2,4-triazino[3,4-*b*][1,2,4,5]-tetrazines. In the preceding communication we described the synthesis of 4-amino-6-methyl-3-methylsulfanyl-4,5-dihydro-1,2,4-triazine-5-thione (**II**) from 4-amino-6-methyl-3-methylsulfanyl-4,5-dihydro-1,2,4-triazin-5-one using silica gel-supported $P_2S_5$ [7]. Nucleophilic replacement of the methylsulfanyl group in the *3*-position or of the thioxo group in the *5*-position of molecule **II** by the action of hydrazine hydrate can produce 3-hydrazino derivative **III** or 5-hyrazino derivative **IV**, respectively. We anticipated that regiochemical control could be accomplished using an appropriate amount of hydrazine hydrate to replace the methylsulfanyl group in the *3*-position rather than the thioxo group in the *5*-position, leading to 4-amino-6-methyl-3-hydrazino-4,5-dihydro-1,2,4-triazine-5-thione (**III**). In fact, this turned out to be the case.

Cyclocondensation of **III** with commercially available ortho esters such as triethyl orthoformate and tri-

**Scheme 1.**




**V**, R = H; **VI**, R = Me.

* The text was submitted by the authors in English.

ethyl orthoacetate in ethanol gave 7-methyl-1,2-dihydro[1,2,4]triazino[3,4-*b*][1,2,4,5]tetrazine-6-thione (**V**) and 1,2-dihydro-3,7-dimethyl-[1,2,4]triazino-[3,4-*b*][1,2,4,5] tetrazine-6-thione (**VI**), respectively.

## EXPERIMENTAL

The melting points were determined on a Reichert apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu spectrometer. The $^1$H NMR spectra were measured on a Bruker instrument at 100 MHz. The mass spectra (electron impact, 70 eV) were obtained on a Varian CH-7 mass spectrometer.

**4-Amino-6-methyl-3-hydrazino-4,5-dihydro-1,2,4-triazine-5-thione (III).** 4-Amino-6-methyl-3-methylsulfanyl-4,5-dihydro-1,2,4-triazine-5-thione (**II**), 0.376 mg (2 mmol), was dissolved in 10 ml of a 1:1 mixture of chloroform with methanol, and 98% hydrazine hydrate, 1 ml (excess), was gradually added to the solution at 0°C. The mixture was stirred for 1 h at room temperature, and the precipitate was filtered off, washed with 10 ml of water, and recrystallized from methanol. Yield 62%, mp 212–213°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.95 s (3H, Me), 5.7 s (2H, $NH_2$, exchangeable with $D_2O$), 7.49 s (2H, $NH_2$, exchangeable with $D_2O$), 11.92 s (1H, NH, exchangeable with $D_2O$). IR spectrum (KBr), ν, cm$^{-1}$: 3550, 3250, 1510, 1420, 1380, 1310, 1280, 1215, 1140, 1080. Mass spectrum, *m*/*z* ($I_{rel}$, %): 172 (3) $[M]^+$, 171 (4), 170 (43), 152 (9), 137 (9), 107 (17), 98 (36), 68 (14), 59 (56), 43 (100), 30 (48).

**7-Methyl-1,2-dihydro[1,2,4]triazino[3,4-*b*]-[1,2,4,5]tetrazine-7-thione (V).** Compound **III**, 344 mg (2 mmol) was dissolved in hot ethanol, triethyl orthoformate, 1 ml (excess), was added to the solution, and the mixture was heated for 1 h under reflux. The mixture was then cooled to room temperature, and the precipitate was filtered off, washed with 10 ml of ethanol, and recrystallized from ethanol. Yield 284 mg (78%), mp 310–311°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.81 s (3H, Me), 6.9 d (1H, CH), 8.93 s (1H, NH, exchangeable with $D_2O$). IR spectrum (KBr), ν, cm$^{-1}$: 3200, 3100, 3000, 1620, 1520, 1460, 1420, 1060, 705, 670. Mass spectrum, *m*/*z* ($I_{rel}$, %):181 (5) $[M]^+$, 179 (100), 124 (7.5), 121 (27), 97 (14), 83 (20), 68 (24), 59 (16), 58 (27), 52 (23), 45 (6), 42 (56), 30 (86).

**3,7-Dimethyl-1,2-dihydro[1,2,4]triazino[3,4-*b*]-[1,2,4,5]tetrazine-7-thione (VI).** Triethyl orthoacetate, 1 ml (excess), was added to a solution of 344 mg (2 mmol) of compound **III** in 10 ml of hot ethanol, and the mixture was heated for 1 h under reflux, the progress of the reaction being monitored by TLC using $CHCl_3$ as eluent. When the reaction was complete, the solvent was evaporated to dryness under reduced pressure, and the residue was subjected to column chromatography on silica gel using chloroform–methanol (94:6) as eluent. Yield 58%, mp 230–231°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.67 s (3H, Me), 1.82 s (3H, Me), 8.9 s (1H, NH, exchangeable with $D_2O$), 11.8 s (1H, NH, exchangeable with $D_2O$). IR spectrum (KBr), ν, cm$^{-1}$: 3200, 3100, 2970, 1640, 1515, 1480, 1380, 1350, 1292, 1260, 1100, 1020, 800. Mass spectrum, *m*/*z* ($I_{rel}$, %): 195 (8) $[M]^+$, 194 (11), 193 (100), 164 (12), 141 (49), 136 (28), 98 (19), 96(26), 55(23).

## REFERENCES


1. Neunhoeffer, H. and Wiley, P.F., *Chemistry of 1,2,3-Triazine, 1,2,4-Triazine, Tetrazine, and Pentazine*, New York: Wiley, 1978.
2. *Progress in Heterocyclic Chemistry*, Gilchrist, T. and Gribble, G.W., Eds., Oxford: Pergamon, 2002, vol. 14.
3. Hu, W.-X., Rao, G.-W., and Sun, Y.-Q., *Bioorg. Med. Chem. Lett*., 2004, vol. 14, p. 1177 (see also references cited therein).
4. Diana, P., Barraja, P., Lauria, A., Montalbano, A., Almerico, A.M., Dattolo, G., and Cirrincione, G., *Bioorg. Med. Chem*., 2003, vol. 11, p. 2371.
5. Di Grandi, M.J., Curran, K.J., Baum, E.Z., Bebernitz, G., Ellestad, G.A., Ding, W.D., Lang, S.A., Rossi, M., and Bloom, J.D., *Bioorg. Med. Chem. Lett*., 2003, vol. 13, p. 3483.
6. Heravi, M.M., Nami, N., Oskooie, H.A., and Hekmat-Shoar, R., *Phosphorus, Sulfur Silicon*, 2005, vol. 180, p. 1873; Heravi, M.M., Montazeri, N., Rahimizadeh, M., Bakavoli, M., and Ghassemzadeh, M., *J. Heterocycl. Chem*., 2005, vol. 42, p. 1021; Heravi, M.M., Nami, N., Oskooie, H.A., and Hekmat-Shoar, R., *Phosphorus, Sulfur Silicon*, 2005, vol. 180, p. 1605; Ghassemzadeh, M., Adhami, F., Taeb, A., Heravi, M.M., and Neumüller, B., *Z. Anorg. Allg. Chem*., 2005, vol. 631, p. 1568; Heravi, M.M., Keivanloo, A., Rahimizadeh, M., Bakavoli, M., Ghassemzadeh, M., and Neumüller, B., *Tetrahedron Lett*., 2005, vol. 46, p. 1607; Heravi, M.M., Keivanloo, A., Rahimizadeh, M., Bakavoli, M., and Ghassemzadeh, M., *Tetrahedron Lett*., 2004, vol. 45, p. 5747.
7. Heravi, M.M., Rajabzadeh, G., Rahimizadeh, M., Bakavoli, M., and Ghassemzadeh, M., *Synth. Commun*., 2001, vol. 31, p. 2231.