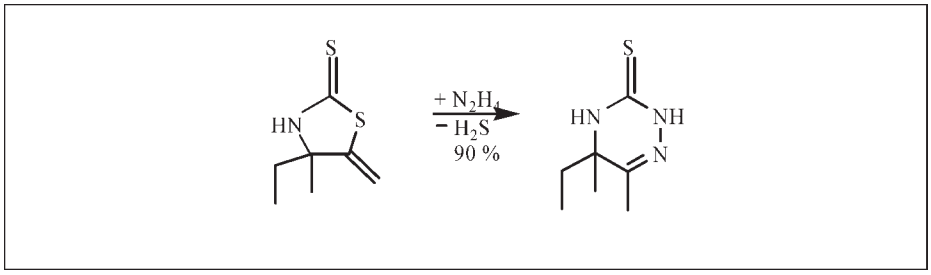
Saifidin Safarov,[a]* Elmurod Pulatov,[a] Muhamacho Amadovich Kukaniev,[a] Heinz Kolshorn,[b] and Herbert Meier[b]

[a]V.I. Nikitin Institute of Chemistry, Dushanbe, Tajikistan
[b]Institute of Organic Chemistry, University of Mainz, D-55099 Mainz, Germany
*E-mail: cafi@mail.ru
Received September 3, 2008
DOI 10.1002/jhet.41
Published online 26 May 2009 in Wiley InterScience (www.interscience.wiley.com).



The treatment of 5-methylene-thiazolidine-2-thione with hydrazine hydrate in boiling dioxane leads in a novel type of ring-expansion reaction to 6-methyl-1,2,4-triazine-3-thione.

J. Heterocyclic Chem., **46**, 552 (2009).

INTRODUCTION

Heterocycles represent the class of compounds that contains the majority of biologically or pharmacologically active substances. A vast number of 1,2,4-triazines [1,2] with antifungal, herbicidal, antibacterial, and tubercolo-static activities have been described. Even on 4,5-dihydro-2*H*-1,2,4-triazine-3-thiones, the Crossfire data bank registers presently more than 900 hits. We present here a new synthetic approach to this ring system.

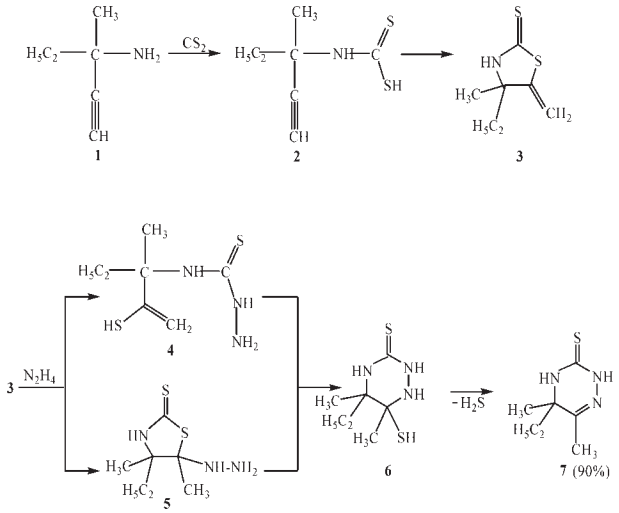
RESULTS AND DISCUSSION

Hennion and Teach [3] published an elegant synthesis of 5-methylene-thiazolidine-2-thiones **3** by the reaction of propargylamines and CS_2 (Scheme 1). The process can be applied to many amines **1** with different substituents [3–8]. We found now that **3** reacts with hydrazine hydrate in ethanol under elimination of H_2S.

Among the variety of conceivable products, we verified the 4,5-dihydro-2*H*-1,2,4-triazine-3-thione structure **7** by one- and two-dimensional NMR studies [HMQC, HMBC]. The (^{1}H,^{15}N) HMBC technique, shown in Figure 1, was the most important tool for the structure determination. Figure 1 depicts the crosspeaks of all expected $^nJ(^1H,^{15}N)$ couplings for $n = 1, 2, 3$. Direct, geminal, and vicinal couplings were observed for 2-H to N-2, N-1, and N-4, respectively. Both diastereotopic methylene protons of the ethyl group on C-5 and the protons of the methyl group on C-5 give vicinal couplings to N-4. The proton on N-4 shows the direct coupling (^1J) to N-4 and a vicinal coupling (^3J) to N-2. Finally, the methyl protons of 6-CH_3 give a ^3J coupling to the sp^2 nitrogen atom N-1. The correlation of the ^{1}H, ^{13}C, and ^{15}N chemical shifts to certain nuclei is presented in Figure 2.

Two possible mechanistic routes for the ring-expansion **3**→**7** are illustrated in Scheme 1. Compound **3** contains C-2 and C-5 as electrophilic centers for the attack of N_2H_4 as nucleophile. The concomitant ring opening to **4**, which represents the hydrazine adduct of an

Scheme 1



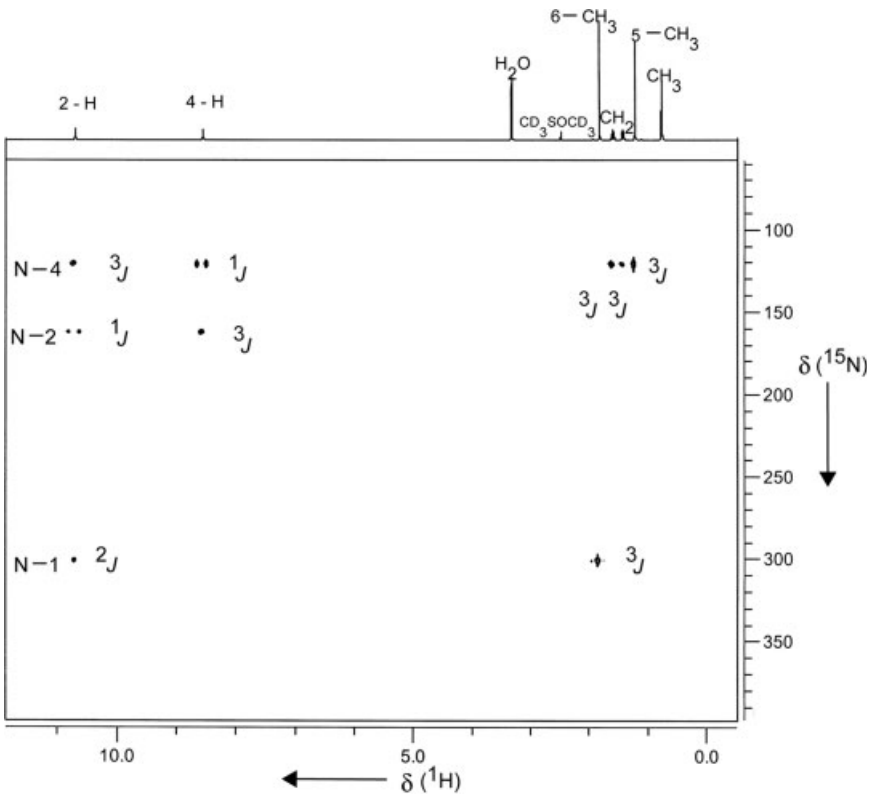


Figure 1. (^{1}H, ^{15}N) HMBC Spectrum of **7** in CD_3SOCD_3.

isothiocyanate, can be followed by a cyclization to the 1,2,4-triazine derivative **6**. The thiosemicarbazid moiety adds thereby to the polar CC double bond of the ene-thiol function. However, a comparably polar CC double bond is already present in **3**, so that **3**→**5** can be the initial step as well. Ring expansion to **6** and elimination of H_2S (**6**→**7**) can terminate the almost quantitative process **3**→**7**.

We are attempting to apply this ring enlargement reaction in order to generate novel mono- and bicyclic 1,2,4-triazine systems with biological or pharmacological activity [9].

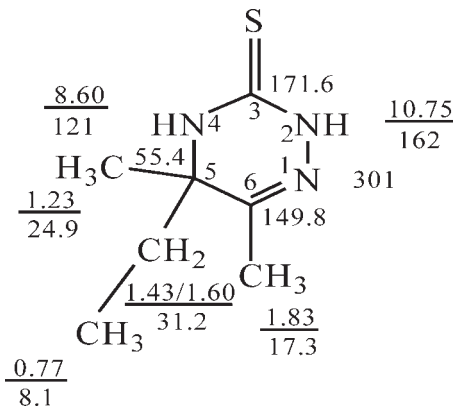


Figure 2. ^{1}H, ^{13}C, and ^{15}N chemical shifts of **7** in CD_3SOCD_3 [δ (^{1}H) and δ (^{13}C) values related to TMS as internal standard, δ (^{15}N) values related to NH_3, H_3CNO_2 as external standard]. Because of the chiral center C-5, the CH_2—CH_3 group gives rise to a ABM_3 spin pattern with multiplets at 1.43 and 1.60 ppm for the CH_2 protons and a triplet at 0.77 ppm for the CH_3 protons.

EXPERIMENTAL

Melting points were measured with a Büchi melting point apparatus. NMR spectra were obtained on Bruker AMX 400 and Avance 600 spectrometers. Mass spectra were recorded on a Finnigan MS 95 (field desorption technique) and a Micromass Q-TOF-ULTIMA API (electrospray technique) spectrometer.

5-Ethyl-5,6-dimethyl-4,5-dihydro-2*H*-[1,2,4]triazine-3-thione (7). To 1.73 g (10.0 mmol) 4-ethyl-4-methyl-5-methylene-thiazolidine-2-thione (**3**) [3] in 10 mL dioxane, 20 mL (2.0 g, 40.0 mmol) hydrazine hydrate (65%) were slowly added within 30 min. The vigorously stirred solution was refluxed for 6 h, cooled to 0°C and diluted with 20 mL crushed ice. The formed precipitate was collected by filtration, washed with water, dried, and recrystallized from ethanol. Yield: 1.54 g (90%), mp: 182°C. FD MS: m/z (%) = 171 (100) [M^+]; ESI HRMS m/z: 172.0910 [M+H^+], calcd. 172.0908. Anal. Calcd. for $C_7H_{13}N_3S$ (171.3): C, 49.09; H, 7.65; N, 24.54. Found: C, 48.88; H, 7.94; N, 24.39.

REFERNCES AND NOTES

[1] Neunhoeffer, H. In Comprehensive Heterocyclic Chemistry; Katritzky, A. R.; Rees, C. W. Eds.; Pergamon Press, Oxford, 1984; Vol. 3, Part 2B, p 385.

[2] Neunhoeffer, H. In Comprehensive Heterocyclic Chemistry II; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.; Eds. Pergamon Press: Oxford, 1996, p 507; Vol. 6. (a) Katritzky, A. R., Ramsden, C.; Scriven, E. F. V.; Taylor, R.; Eds., In Comprehensive Heterocyclic Chemistry III, Elsevier, Amsterdam, 2008; Vol. 9.

[3] Hennionn, G. F.; Teach, E. G. J Am Chem Soc 1953, 75, 4297.

[4] Shi, M.; Shen, Y.-M. J Org Chem 2002, 67, 16.

[5] Isobaev, M. D.; Venger, E. F.; Glazunova, E. M. J Org Chem USSR (Engl Transl) 1986, 22, 875. (a) Isobaev, M. D.; Venger, E. F.; Glazunova, E. M. Zh Org Khim 1986, 22, 978.

[6] Hanefeld, W.; Bercin, E. Liebigs Ann Chem 1985, 58.

[7] Williams, D. R.; Moore, J. L. Tetrahedron Lett 1983, 24, 339.

[8] Yura, Y. Chem Pharm Bull 1962, 10, 1087.

[9] First results showed that the ring-expansion can be realized with 5-methylene-thiazolidine-2-thiones with various substituents in 3- and 4-positon.