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DIRECTION OF ISOMERIZATION OF 5-HYDROXY-3-PROPARGYLTHIO-1,2,4-TRIAZINES ACCORDING TO $^{1}H/^{15}N$ HETERONUCLEAR MULTIPLE BOND CORRELATION (HMBC) SPECTRA

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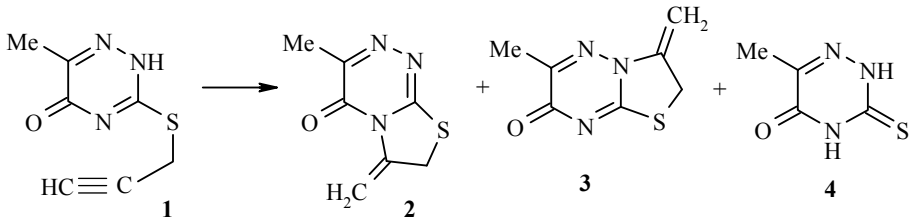
We have studied isomerization of 6-substituted 5-hydroxy-3-propargylthio-1,2,4-triazines using base catalysis. We have used NMR correlation spectroscopy ($^{1}H/^{15}N$ HMBC spectra) to prove the structure of the regioisomer formed. The type of regioisomer formed (3,6-dimethylthiazolo[3,2-b]-1,2,4-triazin-7-one) allows us to say that isomerization occurs as a direct propynyl rearrangement.

Keywords: 5-hydroxy-3-propargyl-1,2,4-triazine, 3-methyl-7H-thiazolo[3,2-*b*]-1,2,4-triazin-7-ones, rearrangement, regioisomer, $^{1}H/^{15}N$ HMBC spectra.

The process of isomerization of aromatic and heterocyclic propargyl ethers and thioethers, in particular the Claisen and Cope rearrangements, has been vigorously studied to date. These processes are of significant preparative importance for obtaining six-membered and five-membered condensed heterocycles. The results of such studies are covered in monographs and reviews [1, 2]. Isomerization of heterocyclic thiopropargyl ethers, especially ones containing several centers at which ring closure is possible, has been studied in significantly less detail than for aromatic ethers. Substituted 5-hydroxy-3-propargylthio-1,2,4-triazines are specifically included among such compounds. The first attempt to discuss the regiochemistry of the process of isomerization of 6-methyl-3-propargyl-1,2,4-triazin-5(2H)-one (**1a**) was made in [3]. The authors tried to determine whether a [3,3]-sigmatropic rearrangement or direct nucleophilic addition of the amide functional group to the acetylene moiety occurred. The reaction was carried out both in aprotic and in protic solvents at their boiling point and in the presence of a Pd(II) complex as the catalyst. According to the results of the study in [3], in the presence of $Pd(PhCN)_2Cl_2$, a mixture of products **2-4** is formed. Compound **3**, as the authors noted, may also be the only product if cyclization is catalyzed by NaOH.



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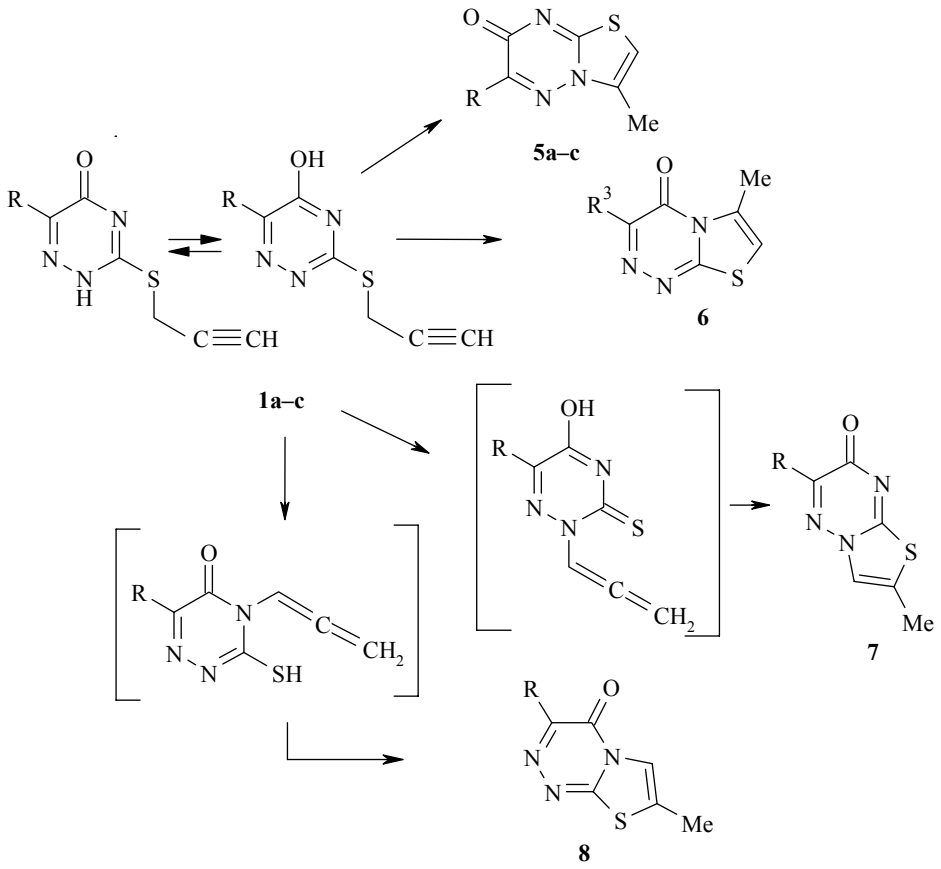
We should note that the authors of [3] isolated the intermediate products **2** and **3**, i.e., the reaction does not reach the step of aromatization of the methylidenethiazoline moiety. This is ensured by using solvents with moderate basicity and a sufficiently long reaction time. To a significant extent, such reaction conditions are probably the reason for the problem of structural identification of the isomers formed. Such identification is based on the ^{1}H NMR spectra: for compound **2**, the chemical shifts of the protons of the *exo*-methylene moiety differ by about 1.4 ppm. For its isomer **3**, the chemical shifts of these signals are not very distinguishable.

In a study of different 6-substituted 5-hydroxy-3-propargylthio-1,2,4-triazines **1a-c**, we also observed that the reaction products have a bicyclic structure, and isomerization in aqueous base occurs practically instantaneously in quantitative yield even at room temperature. With the aim of studying the step-by-step formation of the bicyclic product, we obtained a model compound: propargylthio-1,2,4-triazine **1a**, and studied the process of its cyclization.

Theoretically possible isomerization routes for this compound are shown in the scheme below.

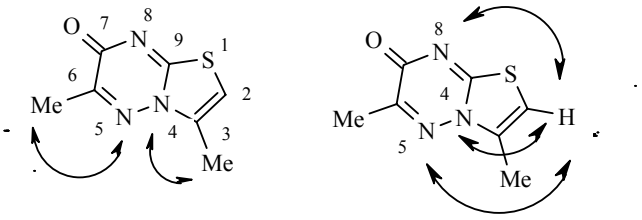


a R = Me, **b** R = Ph, **c** R = 2- $H_2NC_6H_4$

Here we do not consider formation of the product with a thiazine ring rather than a thiazole ring, since analysis of the ^{1}H and ^{13}C NMR spectra allows us to confidently say that closure of a five-membered ring occurs: in the ^{1}H NMR spectrum, the signal at 7.04 ppm corresponds to the aromatic proton of the thiazole ring, and in the ^{13}C NMR spectrum the signals at 103 ppm and 135 ppm correspond to the carbon atoms of the thiazole ring. The structures of compounds **5-8**, which are regioisomers, differ in the position of both the methyl group and the proton of the thiazole ring relative to each of the nitrogen atoms of the triazine ring. Once we have determined which regioisomer is formed, we can establish not only the direction of cyclization (at N(2) or

N(4) of the triazine ring), but also the nature of the isomerization: according to a Claisen type rearrangement, or as a direct propynyl rearrangement.

We know [4, 5] that $^{1}H/^{15}N$ HMBC spectra have been successfully used to solve such problems. Depending on the delay time τ_{mb} selected in the HMBC pulse sequence, in such a spectrum we can observe correlations between nuclear spins through the number of bonds of interest. In the case under consideration, we are interested in the spin–spin coupling constants through three and four bonds: $^{3}J_{(N,H)}$, $^{4}J_{(N,H)}$. According to the data in [6, 7], in substituted six-membered nitrogen-containing heterocycles, $^{3}J_{(N,H)}$ = ~3 Hz while $^{4}J_{(N,H)}$ is ~1 Hz. Thus it is advisable to select the delay time in the $^{1}H/^{15}N$ HMBC experiment corresponding to this interval of spin–spin coupling constants. The scheme below shows the three-bond and four-bond $^{1}H/^{15}N$ correlations for 3,6-dimethyl-7H-thiazolo[3,2-*b*]-1,2,4-triazin-7-one.



The $^{1}H/^{15}N$ HMBC correlation spectra are shown in Fig. 1. In these spectra, we can observe cross peaks arising due to interaction between the aromatic protons of the thiazole ring and N(5) (7.04 for F1 and -64 ppm for F2), N(8) (7.04 for F1 and -146 ppm for F2) and N(4) (7.04 for F1 and -170 ppm for F2) and cross peaks from interaction between protons of the methyl groups at the atoms C(6) and N(5) (2.27 for F1 and -60 ppm for F2), and also at C(3) and N(4) (2.37 for F1 and -170 ppm for F2).

Thus the correlations observable in the $^{1}H/^{15}N$ HMBC spectrum of 3,6-dimethyl-7H-thiazolo[3,2-*b*]-1,2,4-triazin-7-one for protons of the methyl groups allow us to pick out two possible structures (**5** and **6**) among the four possible structures. For the aromatic proton of the thiazole ring, we observe three correlation peaks in the spectrum; since the spectrum recording conditions allow us to observe correlations only through three and four bonds, we can unambiguously give preference to structure **5**.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were taken on a Bruker DPX-300 spectrometer (300 MHz and 75 MHz respectively) in DMSO-d_6. The chemical shifts were measured relative to the residual solvent signal (in the ^{1}H spectrum, at 2.50 ppm; in the ^{13}C spectrum, at 39.6 ppm). Correlations of the ^{1}H and ^{15}N chemical shifts through long-range spin–spin coupling constants were obtained by the HMBC method on a Bruker AMX-500

TABLE 1. $^{1}H/^{15}N$ Correlations Found in the $^{1}H/^{15}N$ HMBC Spectrum of 3,6-Dimethyl-7H-thiazolo[3,2-*b*]-1,2,4-triazin-7-one (**5a**)

NMR spectrum, δ, ppm						Reaction route
^{15}N			^{1}H			
N(5)	N(8)	N(4)	6-CH_3	3-CH_3	2-CH_3	
-60	-140	-170			7.04	N5↔H2, N8↔H2, N4↔H2
		-170		2.36		N4↔C3-CH_3
-60			2.27			N5↔C6-CH_3

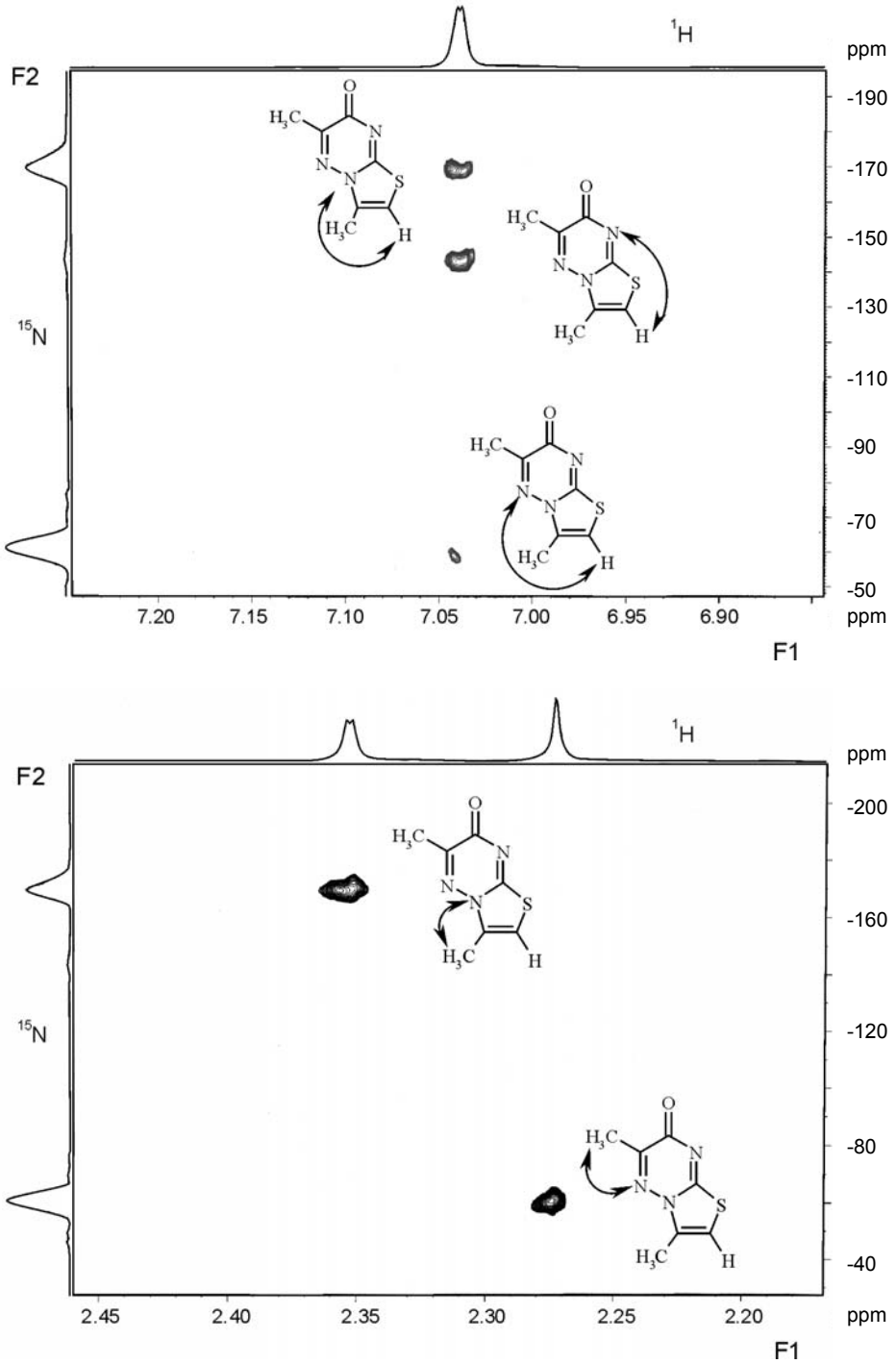


Fig. 1. ^{1}H/^{15}N HMBC spectrum of 3,6-dimethyl-7H-thiazolo[3,2-*b*]-1,2,4-triazin-7-one.

spectrometer (500 MHz for ^{1}H and 50 MHz for ^{15}N respectively) using a 5-mm inverse detection probe (4 wt.% solution in DMSO-d_6 at room temperature). To improve the sensitivity and eliminate artifacts connected with phase cycling, we used a modified HMBC pulse program using gs-HMBC pulsed field gradients [8-10] (invietgs in the Bruker program library). The holding time (d4 in this program) was taken as equal to 0.109 sec, which

corresponds to the proposed spin–spin coupling constant J = 2.3 Hz. A sufficient signal-to-noise ratio was achieved for 16 repetitions in each of the 68 experiments. The spectral ranges were 3822 Hz for ^{1}H and 19212 Hz for ^{15}N. In the ^{15}N spectrum, the chemical shifts were measured relative to liquid NH_3 (0 ppm at 25°C).

3,6-Dimethyl-7H-thiazolo[3,2-*b*]-1,2,4-triazin-7-one (5a). Triazine **1a** (1 g, 5.5 mmol) was dissolved at room temperature in a 9% aqueous solution of NaOH (15 ml). By 1 min later, a white precipitate began to form; the reaction mixture was allowed to stand for 2-3 h, after which the precipitate was filtered out, washed with water, and recrystallized from ethanol. Yield 0.7 g (70%). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.28 (3H, s, C$\underline{H}_3$); 2.37 (3H, d, ^{4}J = 1, C$\underline{H}_3$); 7.04 (1H, q, ^{4}J = 1, H-2). ^{13}C NMR spectrum, δ, ppm: 13.0 (C$\underline{H}_3$); 18.2 (C$\underline{H}_3$); 103.9 (C-2); 135.2 (C-3); 152.9 (C-6); 159.4 (C-7); 164.8 (C-9).

3-Methyl-6-phenyl-7H-thiazolo[3,2-*b*]-1,2,4-triazin-7-one (5b) was obtained analogously starting from 5-hydroxy-6-phenyl-3-propargylthio-1,2,4-triazine. Yield 75%. ^{1}H NMR spectrum, δ, ppm: 2.5 (3H, s, C$\underline{H}_3$); 7.05 (1H, s, H-2); 7.5 (3H, m, Ar); 8.2 (2H, m, Ar). ^{13}C NMR spectrum, δ, ppm: 12.5 (C$\underline{H}_3$); 104.1 (C-2); 127.6, 128.9, 130.2, 132.2, 134.5 (C-3); 147.8 (C-6); 157.3 (C-7); 163.2 (C-9).

6-(2'-Aminophenyl)-3-methyl-7H-thiazolo[3,2-*b*]-1,2,4-triazin-7-one (5c). A solution of 6-(2'-aminophenyl)-5-hydroxy-1,2,4-triazine-3-thiol (1 g, 4.5 mmol) in 9% aqueous KOH (10 ml) was stirred with propargyl chloride (0.35 g, 4.7 mmol) for 3 h at ~20°C. The precipitate formed was separated after 12 h and recrystallized from ethanol. Yield 0.8 g (69%). ^{1}H NMR spectrum, δ, ppm: 2.4 (3H, s, C$\underline{H}_3$); 5.4 (2H, s, N$\underline{H}_2$); 6.6 (1H, t, J = 7.6, J = 8.1); 6.75 (1H, d, J = 9.1); 7.05 (1H, s, H-2); 7.15 (1H, t, J = 7.4, J = 7.6); 7.5 (1H, d, J = 8.5). ^{13}C NMR spectrum, δ, ppm: 13.7 (C$\underline{H}_3$); 104.7 (C-2); 116.2, 117.1, 117.2, 131.4, 131.9, 135.8 (C-3); 148.7 (C-6); 151.7, 158.7 (C-7); 164.0 (C-9).

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