Mechanism of dehydration of 2-CH_2R- and 2-CHR_2-4-hydroxy-Δ^2-thiazolines as intermediates in the Hantzsch thiazole synthesis and factors impeding the synthesis of 2-Me-, 2-Ar-, and 2-Het-substituted thiazoles and thiazolo[5,4-*b*]indoles

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Based on the results of studies of the deuterium exchange and dehydration of 4-hydroxy-Δ^2-thiazolines and 2-R-4-acetyl-8b-hydroxy-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indoles containing the α-methylene (methine) unit at the C(2) atom, the mechanism of dehydration of these compounds generated as intermediates in the Hantzsch synthesis of thiazoles and 2-R-4-acetyl-4*H*-thiazolo[5,4-*b*]indoles was proposed. This mechanism includes an additional step of the formation of the corresponding Δ^3-thiazolines. According to the results of quantum chemical calculations, this is energetically more favorable than the dehydration in terms of the commonly accepted mechanism. In some cases, an acidic medium impedes the dehydration of 4-hydroxy-Δ^2-thiazolines or their cyclic analogs. The proposed mechanism provides an explanation for the empirical data on the differences in the reactivities of both thioamides and α-haloketones, which have remained unexplained in terms of the commonly accepted mechanism. The spontaneous thiazole synthesis is virtually impossible starting from thioamides of aromatic or heteroaromatic acids and α-haloketones bearing electron-withdrawing α´ substituents or cyclic bromoindoxyl-type haloketones. In the thiazole synthesis from these starting components, it is expedient to perform dehydration under basic catalysis.

Key words: thiazoles, 2-R-thiazolo[5,4-*b*]indoles, Hantzsch reaction, deuterium exchange, 4-hydroxy-Δ^2-thiazolines, 2-R-4-acetyl-8b-hydroxy-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indoles, dehydration, Δ^3–thiazolines, isomerization, cations, quantum chemical calculations, DTF-PBE.

In our previous publication,[1] it has been shown that the structures of α-haloketones and thioamides have a substantial effect on the course of the Hantzsch reaction (the importance of this reaction in modern studies was considered in the publication[2]) and, in some cases, ensure complete inhibition of the thiazole synthesis.[3] However, the factors responsible for the abnormal course of this reaction, which produces 4-hydroxy-Δ^2-thiazolines or 4-acetyl-2-R-8b-hydroxy-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indoles instead of thiazoles or 2-R-4-acetyl-4*H*-thiazolo[5,4-*b*]indoles (Hantzsch reaction products) from some α-haloketones and thioamides, remain unclear. It is known that not nearly all 4-hydroxy-Δ^2-thiazolines or their heterocyclic analogs, which are intermediates in the thiazole synthesis, can undergo dehydration under these reaction conditions or even under more drastic conditions.[4,5] The Me, Ar, and Het substituents at position 2 of the hydroxythiazoline ring impede or completely inhibit the dehydration, whereas substituents containing the α-methylene (methine) unit at the C(2) atom substantially facilitate the reaction. The above-considered data cannot be explained in terms of the commonly accepted mechanism of the Hantzsch reaction.[6,7]

It is reasonable to expect that the scope of this reaction would be broadened if one will answer the questions as to why the dehydration of intermediate hydroxy compounds is the rate-determining step in the thiazole synthesis only in some cases and whether it is possible, based on the nature of the substituents at the C(2) atom of the hydroxythiazoline ring, to know in advance whether the dehydration will be spontaneous or it will require special conditions. For this purpose, we investigated the distin-

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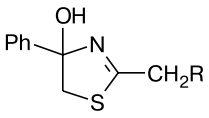
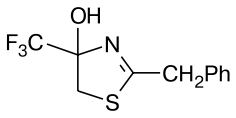
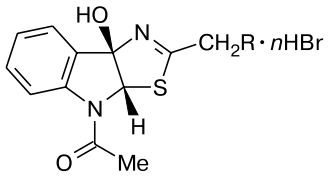
guishing features of the mechanism (the so-called gross mechanism according to March[8a]) of dehydration of intermediate 4-hydroxy-Δ^2-thiazolines and 2-R-4-acetyl-8b-hydroxy-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indoles containing various substituents at position 2 of the hydroxythiazoline ring. Apparently, the question about the influence of the nature of substituents (2-CH_3, 2-CH_2R, and 2-CHR_2) reduces to the question about the prototropic transformations of the protons in these substituents. To tackle this question, we monitored the deuterium exchange in 2-methyl- and 2-benzylhydroxythiazolines, their indole analogs, and the dehydration products of the latter by ^{1}H NMR spectroscopy and mass spectrometry. In addition, we studied the pathway of dehydration of intermediate hydroxy compounds, which differ in the nature of the substituents at positions 2, 4, and 5 of the hydroxythiazoline ring, under standard and milder conditions. We investigated 2-methyl- and 2-benzyl-4-hydroxy-Δ^2-thiazolines **1a—c**, 4-acetyl-8b-hydroxy-2-methyl-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indole (**1d**), and 4-acetyl-2-benzyl-8b-hydroxy-3a,8b-dihydro-4*H*-thiazolo[5,4-*b*]indole hydrobromide (**1e**) as intermediates in the synthesis of the corresponding thiazoles **2a—c** and thiazolo[5,4-*b*]indoles **2d,e**.



1a,b



1c

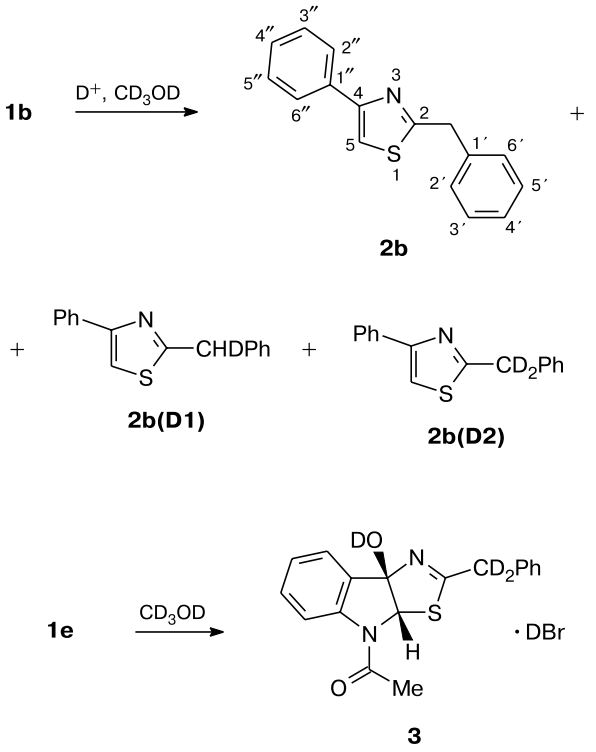


1d,e

1: R = H (**a**, **d**), Ph (**b**, **e**); *n* = 0 (**d**), 1 (**e**)

In the course of dissolution in the DMSO-d_6—CD_3OD—D_2O—DCl system used for the monitoring, hydroxythiazoline **1b** was transformed into thiazoles **2b**, **2b(D1)**, and **2b(D2)** (Scheme 1). The ratio between monodeuterated, dideuterated, and nondeuterated thiazoles **2b(D1)** : **2b(D2)** : **2b** was ~55 : 10 : 35. At the same time, it should be taken into account that the deuterium exchange can be influenced by water that is eliminated upon dehydration and is present in deuterated solvents. The degree of deuterium exchange was determined by comparing the integrated intensities of the signals for the protons of the 2-CH_2 and 2-CHD groups with the constant integrated intensities of the signals for the aromatic protons in the ^{1}H NMR spectra of compounds **2a**, **2b**, and **1e** (6 H, 11 H, and 9 H, respectively). The percentage of dideuterated compound **2b(D2)** was calculated as the difference between 100% and the total percentage of **2b** and **2b(D1)**. Special experiments showed that the deuterium exchange of the methyl and methylene protons of the 2-CH_2R groups in thiazoles **2a,b,e** in a DMSO-d_6—CD_3OD—D_2O—DCl solution at ~20 °C for 1 h is negligible.

Scheme 1



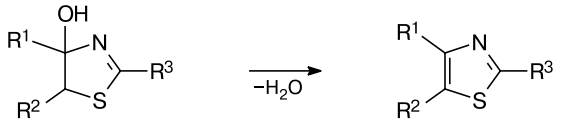
Upon dissolution in DMSO-d_6—CD_3OD (5 : 1, v/v), hydroxy compounds **1a,e** remain unchanged, which allowed the estimation of the deuterium exchange rate in each case. The deuterium exchange of both methylene protons of the CH_2Ph group in hydrobromide **1e** was found to occur in solution rather rapidly to form dideuterated (2-CD_2Ph) hydrobromide **3** (see Scheme 1); the half-exchange time was ~10 min. No signals of the dehydration product were observed in the NMR spectrum of deuterated derivative **3** upon storage of this solution for 1—2 h.

Unlike compound **1e**, hydroxythiazoline **1a** is subjected to dehydration in a DMSO-d_6—CD_3OD—D_2O—DCl solution to give thiazole **2a**; the half-life period was approximately equal to 15 min. In the course of the complete transformation of hydroxythiazoline **1a** into thiazole **2a**, ~3.5% of the total amount of the protons in the Me groups were subjected to the deuterium exchange. An analysis of these results showed that, under the experimental conditions in an

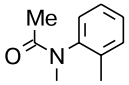
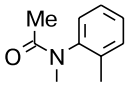
acidic medium, the rate of deuterium exchange of the protons in the 2-CH_2R substituent substantially depends on the nature of this substituent (R = H or Ph in hydroxy compounds **1a** and **1b**,**e**, respectively). It was also found that the rate of deuterium exchange in 2-benzyl-substituted hydroxy compounds **1b**,**e** is substantially higher than that in 2-methyl-4-hydroxythiazoline **1a**.

In addition, we compared the dehydration rates under analogous conditions (Scheme 2) for 2-methyl-substituted compounds **1a**,**d**, on the one hand, and 2-$CH_2R(CHR_2)$-hydroxy compounds **1b,c,e—g**, on the other hand.

Scheme 2



1, 2	R^1	R^2	R^3
a	Ph	H	Me
b	Ph	H	CH_2Ph
c	CF_3	H	CH_2Ph
f	Ph	H	CH_2-3-indolyl
g	Ph	H	$CHPh_2$

1, 2	$R^1 + R^2$	R^3
d		Me
e		CH_2Ph

Hydroxy compounds **1b,e—g** are subjected to dehydration by heating in ethanol in the presence of mineral acids (HCl or HBr) for 1 min to give thiazoles **2b,f,g** and thiazoloindole **2e** in high yields.[1] Under analogous conditions, 2-benzyl-4-hydroxy-4-trifluoromethyl-Δ^2-thiazoline (**1c**) is transformed into thiazole **2c** in a yield of only 29% (according to TLC, the dehydration of hydroxythiazoline **1c** was completed when the heating time was increased to 15 min; the yield of thiazole was 74%).[1] Under the same conditions, 2-methyldihydrohydroxythiazoloindole **1d** is not subjected to dehydration at all. According to the published data,[2,9] 2-methylhydroxythiazolines, which were prepared by the reactions of thioacetamide with bromoacetophenone and trifluorobromoacetone, underwent dehydration under much more drastic conditions to give thiazoles. For example, hydroxythiazoline **1a** was transformed into 2-methyl-4-phenylthiazole (**2a**) by refluxing in acetic acid.[9] We showed that this dehydration proceeds also under milder conditions, *i.e.*, on heating of hydroxythiazoline **1a** in Pr^iOH in the presence of an equimolar amount of HCl for 20 min. Therefore, the dehydration of 4-hydroxy-2-methyl-Δ^2-thiazolines requires longer time than the dehydration of 2-benzyl-4-hydroxy-Δ^2-thiazolines, which is evidenced, in particular, by an increase in the duration of dehydration of 2-methylhydroxythiazoline **1a** by more than an order of magnitude compared to the dehydration of 2-benzylhydroxythiazoline **1b**.

A comparison of the results of the deuterium exchange and dehydration of hydroxy compounds **1a,b,e** in an acidic medium showed that 2-benzylhydroxythiazoline **1b** is characterized by a high rate of the deuterium exchange of protons in the 2-CH_2R substituent and an exceptionally high rate of dehydration giving rise to thiazole. 2-Benzylhydroxydihydrothiazoloindole **1e**, in which the deuterium exchange of methylene protons occurs at a high rate, is also subjected to dehydration to give thiazoloindole, although the duration of its dehydration is greater than that observed in the above-considered case. 2-Methylhydroxythiazoline **1a** is characterized by a low rate of the deuterium exchange of methyl protons. However, according to our data, compound **1a** is rather easily dehydrated in an acidic medium. Therefore, there are substantial differences in the rates of both the deuterium exchange and the dehydration of the corresponding hydroxy compounds. The ease of dehydration of compounds **1b,e** and the high rate of deuterium exchange of methylene protons are indicative of the involvement of these protons in prototropic transformations associated, apparently, with the formation of the corresponding methylene bases.[10] Compounds having such structures, dimeric and monomeric methylene bases based on quaternary benzothiazolium salts, have found wide use in the synthesis of merocarbocyanine dyes.[11,12] The synthesis of monomeric 2-methylene-3-methylbenzothiazoline by the reaction of tetramethylguanidine with 2,3-dimethylbenzothiazolium *p*-toluenesulfonate was documented.[13] In the presence of trace amounts of acids, dimeric 3-methyl-2-methylenebenzothiazoline is known to exist in equilibrium with the monomer, and the deuterium exchange of methylene and methine protons, respectively, occurs in these bases immediately after the addition of D_2O.[11] For comparison, the deuterium exchange of protons of the $C(2)H_3$ group in 2-(2,3-dimethylbenzothiazol-2-yl)methylene-3-methylbenzothiazoline derived from 2,3-dimethylbenzothiazolium methyl sulfate proceeds under more drastic conditions[11] (under the action of D_2O in pyridine 20 °C at 48 h).

According to the above data, the high rate of deuterium exchange in hydroxythiazoline **1b** observed in an acidic medium can be attributed to the involvement of methylene base **4b** in this process (Scheme 3). Apparently, under the conditions of our experiment, the corresponding base is formed from hydroxythiazoline **1a** in a small amount due to which its contribution to the deuterium exchange is insignificant. Methylene bases can play the key role in the dehydration of 2-benzylhydroxythiazolines **1**, in particular, of **1b** and **1e**, as well as of the previously described[1] hydroxythiazolines **1f,g** containing the methylene or methine unit at position 2. To validate

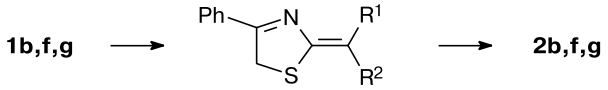
Table 1. Yields, physicochemical characteristics, elemental analysis data, mass-spectrometric data, and the results of IR and ^{1}H NMR spectroscopy for Δ^3-thiazolines **4b,f,g**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	S	Molecular formula	M^+	IR, ν/cm^{-1} NH	C=N	^{1}H NMR, δ 5-H_2 (s, 2 H)	2-CH (s, 1 H)	4-Ph	R^1 (R^2)
4b	58	163—165*	76.58 76.49	5.27 5.18	5.61 5.57	12.72 12.75	$C_{16}H_{13}NS$	251	—	1605	4.96	7.11	7.99 (d, 2 H, J = 8.0); 7.55 (m, 3 H)	7.55, 7.42 (both m, 2 H each); 7.23 (m, 1 H)
4f	49	189—191*	74.35 74.48	4.91 4.83	9.66 9.66	11.17 11.03	$C_{18}H_{14}N_2S$	290	3390	1615	4.91	7.33	7.96 (m, 2 H); 7.52 (m, 3 H)	11.45 (s, NH); 7.05—7.95 (5 H, indole)
4g	51	146—149*	80.59 80.73	5.30 5.20	4.21 4.28	9.89 9.79	$C_{22}H_{17}NS$	327	—	1590	4.74	—	7.91 (d, 2 H, J = 8.0); 7.20—7.55 (m, 3 H)	7.20—7.55 (m, 10 H)

* With decomposition.

this hypothesis, we performed the dehydration of 2-CH_2R(2-CHR_2)-hydroxythiazolines **1b,f,g** under milder conditions than those required for their transformation into thiazoles. As expected, hydroxythiazolines **1b,f,g** were transformed into Δ^3-thiazolines **4b,f,g** in 49—58% yields upon their storage in dioxane with an equimolar amount of acetic acid at 20 °C for 12 h (method *A*) (Table 1, see Scheme 3). According to TLC, the reaction mixture contained also small amounts of thiazoles **2b,f,g**.

Scheme 3



4b,f,g

4: R^1 = Ph, R^2 = H (**b**); R^1 = 3-indolyl, R^2 = H (**f**), R^1 = R^2 = Ph (**g**)

Δ^3-Thiazoline **4b** can also be synthesized in 67% yield by the reaction of bromoacetophenone with thioamide of phenylacetic acid and triethylamine in Me_2CO at ~20 °C for 8 h without the isolation of intermediate hydroxythiazoline **1b** (method *B*). In addition, Δ^3-thiazoline **4b** can be prepared from hydroxythiazoline **1b** by the reaction with a suspension of $Et_2NH \cdot HCl$ in Me_2CO (method *C*). The ^{1}H and ^{13}C NMR spectroscopic data show that Δ^3-thiazolines **4b,f,g** are formed as a single geometric isomer. Compound **4b** has a *Z* configuration (X-ray diffraction data).

The X-ray diffraction structure of molecule **4b** is shown in Fig. 1. Compound **4b** crystallizes in the chiral space

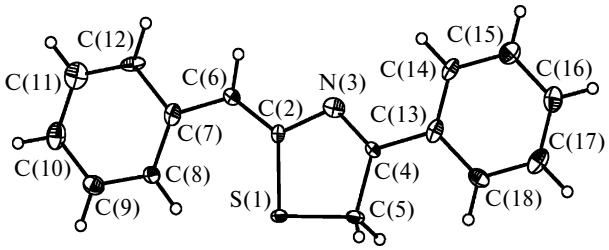


Fig. 1. Overall view of molecule **4b** represented by displacement ellipsoids (p = 50%).

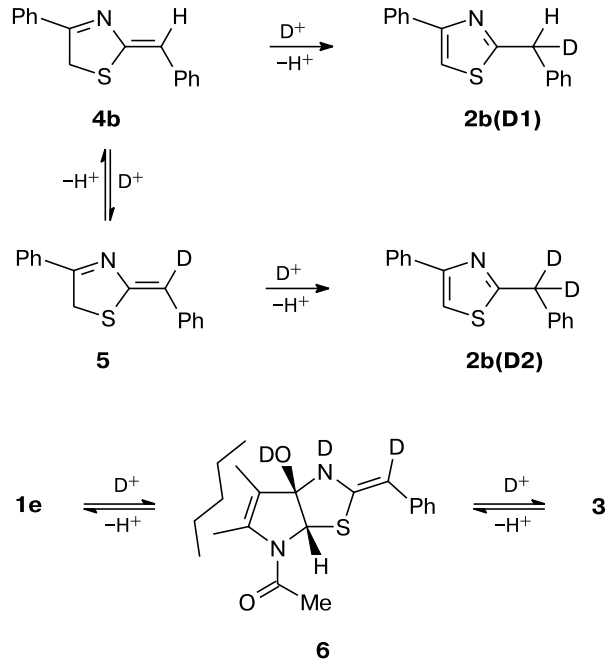
group $P2_1$ with two independent molecules per asymmetric unit. In the crystal, both molecules are planar and have the *Z* configuration. It should be noted that one of the independent molecules exists as a superposition of two *Z* isomers, which are related by a pseudocenter of symmetry lying on the N(3)—C(4) bond. The presence of this disorder and, as a consequence, the weak reflection ability of the crystal do not allow the detailed analysis of the molecular geometry and the crystal packing.

Δ^3-Thiazolines **4b,f,g** are, in turn, easily subjected to isomerization into thiazoles **2b,f,g** by heating in Pr^iOH in the presence of an equimolar amount of HCl over a short period of time. The isomerization product is formed in a virtually quantitative yield. Under the same conditions, hydroxythiazolines **1a,c** and hydrobromide **1e** are transformed into thiazoles **2a,c** and thiazoloindole **2e**, respectively (TLC data), but at a substantially lower rate.

The study of the rate of deuteration of methylene base **4b** in a DMSO-d_6—CD_3OD—DCl—D_2O solution in an NMR tube showed that the deuteration proceeds already in the course of dissolution of the sample, which is accompanied by the transformation of Δ^3-thiazoline **4b** into

a mixture of monodeuterated, dideuterated, and nondeuterated thiazoles **2b(D1)**, **2b(D2)**, and **2b** (Scheme 4).

Scheme 4



In addition, we performed the following two reactions accompanied by the deuterium exchange: the dehydration of 2-benzyl-4-hydroxy-4-phenyl-Δ^2-thiazoline (**1b**) giving a mixture of thiazoles **2b**, **2b(D1)**, and **2b(D2)** and the isomerization of 2-benzylidene-4-phenyl-Δ^3-thiazoline (**4b**), which also produces a mixture of the above-mentioned thiazoles. Both reactions were carried out under virtually the same conditions by heating the starting compounds in a 9 : 1 EtOD—EtOH solution containing an equimolar amount of DCl in D_2O over a short period of time. Crystalline mixtures of deuterated and nondeuterated products were isolated after the treatment of the reaction mixture with aqueous NH_3 to pH = 8. This allowed the comparison of the yields of products with different degrees of deuteration obtained in both reactions. The percentage of each product determined by ^{1}H NMR spectroscopy and mass spectrometry (Table 2) was similar in both reactions. As can be seen from Table 2, both the dehydration of hydroxythiazoline **1b** and the isomerization of Δ^3-thiazoline **4b** afford the same compounds **2b, 2b(D1)**, and **2b(D2)** but in different ratios. The dehydration gives approximately 60% of deuterated thiazoles and 40% nondeuterated thiazole, whereas the isomerization of Δ^3-thiazoline **4b** affords the same products in 80 and 20% yields, respectively (see Table 2). It should be noted that the above-given compositions of the mixtures of dehydration products of hydroxythiazoline **1b**

Table 2. Percentage of thiazoles **2b**, **2b(D1)**, and **2b(D2)** in a mixture prepared by dehydration of hydroxythiazoline **1b** (*A*) or isomerization of Δ^3-thiazoline **4b** in the $C_2H_5OD—C_2H_5OH—D_2O—DCl$ system (*B*) determined by ^{1}H NMR spectroscopy (I) and mass spectrometry (II)

Thiazole	Molecular formula	M^+	Fraction (%)			
			A		*B*	
			I	II	I	II
2b	$C_{16}H_{13}NS$	251	39	41	20	24
2b(D1)	$C_{16}DH_{12}NS$	252	50	50	72	69
2b(D2)	$C_{16}D_2H_{11}NS$	253	11	9	8	7

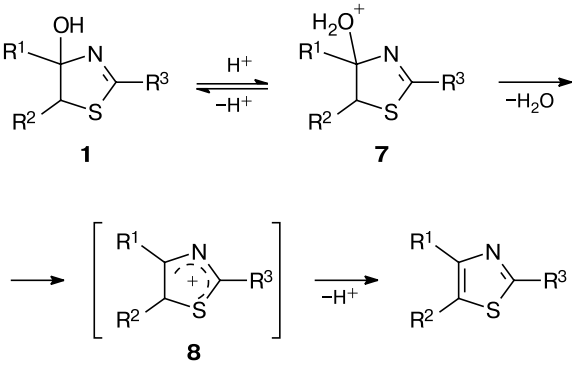
appeared to be similar to the data obtained when this reaction was performed in an NMR tube (see Scheme 1). The fact that the deuteration of Δ^3-thiazoline **4b** affords mono- and dideuterated thiazoles **2b(D1)** and **2b(D2)** apparently indicates that Δ^3-thiazoline **4b** exists in an acidic medium in equilibrium with monodeuterated Δ^3-thiazoline **5**, which undergoes isomerization after the attachment of a deuteron to give dideuterated thiazole **2b(D2)** (see Scheme 4). By analogy, it can be suggested that monodeuterated methylene base **6** is involved in the formation of dideuterated compound **3**. Since compound **3** remains nondehydrated under the experimental conditions, it is clear that the deuteration rate is much higher than the dehydration rate (see Schemes 1 and 4).

Therefore, thiazoles **2b,f,g** are generated from both hydroxythiazolines **1b,f,g** and Δ^3-thiazolines **4b,f,g**. Hence, the latter can be considered as intermediates in the thiazole synthesis from α-haloketones and thioamides containing the α-methylene (methine) unit. The results of deuteration of compound **1e** suggest that, in an acidic medium, this compound initially undergoes isomerization into the corresponding methylene base, which is subjected to dehydration giving rise to Δ^3-thiazoline followed by isomerization of the latter into thiazoloindole **2e**.

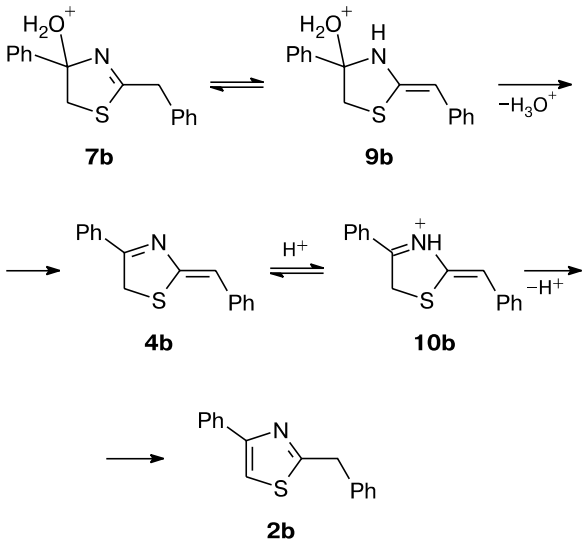
These results cannot be interpreted in terms of the classical mechanism of the Hantzsch reaction, which involves the formation and dehydration of intermediate hydroxythiazolines **1** (Scheme 5).[14] It is assumed that the *O*-protonated form of hydroxythiazoline **7** undergoes dehydration followed by elimination of the proton from position 5, the reaction medium turning acidic as a result of elimination of 1 equiv. of hydrogen halide.[14]

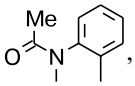
This mechanism provides an explanation for the relationship between the structure of the starting α-haloketone and the ease of dehydration of hydroxythiazoline derived from the starting compound. The fact that 4-hydroxy-2-methyl-4-trifluoromethyl-Δ^2-thiazoline and dihydrohydroxythiazoloindole **1d** are difficult to subject to dehydration can be explained in terms of the hindered cation mechanism of dehydration of tertiary alcohols. The

Scheme 5



Scheme 6

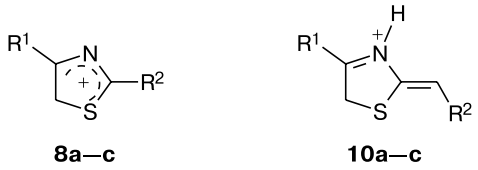


dehydration of these compounds should afford relatively unstable cations **8**, which are destabilized by the electronic ($R^1 = CF_3$) or steric effect of the substituent ($R^1 + R^2 =$  , see Scheme 5). The hindered elimination in ring systems according to Bredt's rule[8b] is attributed to instability of intermediate cyclic cations of type **8**. However, the classical mechanism does not take into account the influence of the nature of the substituent R^3 at position 2 of hydroxythiazolines **1** on the ease of their dehydration and does not explain why the dehydration of compounds **1b,c,e—g** giving rise to thiazoles proceeds much more easily than the dehydration of compounds **1a,d**.

The exceptional ease of dehydration of 2-CH_2R(2-CHR_2)-4-hydroxythiazolines and their analogs can be explained in terms of the following mechanism using compound **1b** as an example.

In an acidic medium, the starting hydroxythiazoline exists in equilibrium with classical hydroxonium cation **7b** (see the classical mechanism of dehydration, Scheme 5) and enamine hydroxonium cation **9b**. The latter is transformed into Δ^3-thiazoline **4b** accompanied by elimination of hydroxonium (Scheme 6). It should be noted that the proton of the thiazole nitrogen atom, which is more acidic than the proton at the C(5) atom, is involved in elimination of hydroxonium. The subsequent protonation and deprotonation of Δ^3-thiazoline **4b** afford the final thiazole. Therefore, the dehydration of 2-$CH_2Ph(CHPh_2)$-4-hydroxythiazolines produces azadiene cations of type **10b**, which are isomeric with cations **8** and are more stable than the latter. This is also consistent with the data on the deuterium exchange in compounds **1b,e**, in which the deuterium exchange occurs at a higher rate than that in 4-hydroxy-2-methylthiazoline **1a**.

The calculations for isomeric cations **10b** and **10c**, **8b** and **8c** by the DFT-PBE method showed that the former cations are more stable than the latter by ~9 and 3 kcal mol^{-1}, respectively. To the contrary, the formation of cation **10a** would be energetically less favorable by ~5 kcal mol^{-1}.



8,10: R^1 = Ph, R^2 = H (**a**), R^1 = Ph, R^2 =Ph (**b**), $R^1 = CF_3$, R^2 = Ph (**c**)

Therefore, the results of calculations confirm the proposed mechanism of dehydration of 2-RCH_2(2-R_2CH)-4-hydroxythiazolines.

Since the yields of the deuterated products in the isomerization of Δ^3-thiazoline **4b** appeared to be higher than those in the transformation of hydroxythiazoline **1b** into thiazole **2b** (see Table 2), it cannot be ruled out that the latter process is accompanied by the partial dehydration of the starting hydroxythiazoline according to the classical mechanism. At the same time, this fact can be attributed to other factors, for example, to those accounting for the influence of the reaction conditions, including the presence of water.

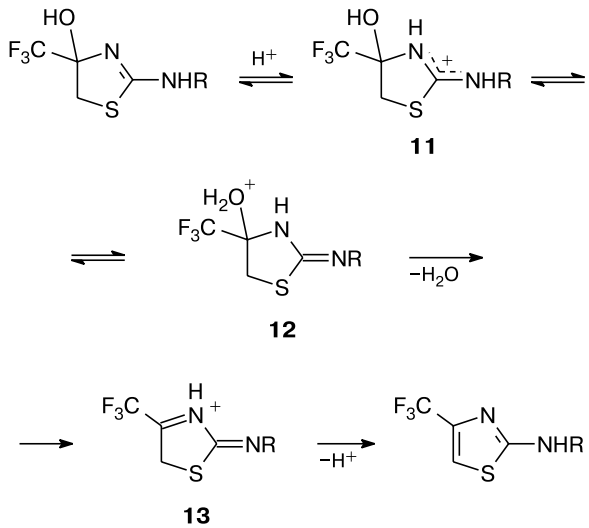
Since the formation of Δ^3-thiazolines from 4-hydroxy-Δ^2-thiazolines facilitates dehydration of the latter, the spontaneous Hantzsch reaction of α-haloketones with thioamides containing the α-methylene (methine) unit is, apparently, attributed to the involvement of Δ^3-thiazolines in this process. The mechanism of isomerization of Δ^3-thiazolines calls for a special investigation. It should be taken into account that such methylene bases rapidly and reversibly bind these reagents at the exocyclic C=C

bond in the presence of water, alcohols, hydrogen halides, *etc*.[12]

The scope of the proposed mechanism of dehydration of hydroxythiazolines would be extended to hydroxythiazolines containing the α-methylene (methine) unit at position 2, in which the substituents can stabilize the resulting azadiene cations of type **10**. In particular, hydroxythiazolines, which we have synthesized by the reaction of haloketones with thioamides of phenylacetic, 3-indolylacetic, diphenylacetic, cyanoacetic, and 3-phenylpropionic acids,[1,5] satisfy this condition. To the contrary, only the classical mechanism of dehydration accompanied by elimination of the proton from position 5 is possible for 2-aryl(hetaryl)-substituted 4-hydroxy-Δ^2-thiazolines, which undergo dehydration in an acidic medium only under relatively drastic conditions. Evidently, the reactions of 2-methylhydroxythiazolines, from which methylene bases are difficult to synthesize, also proceed by this mechanism (see the data on the deuterium exchange and the results of quantum chemical calculations).

The proposed mechanism provides an explanation for the earlier observed[4] ease of formation of 2-aminothiazoles from α,α,α-trifluoro-α′-bromoacetone and thiourea or phenylthiourea (Scheme 7). Apparently, the transformation of immonium cations **11** and **12** into conjugated immonium cations **13** (aza analogs of cation **10**, see Scheme 6) is the key step of dehydration. The final step of the process involves the isomerization of cations **13** into 2-aminothiazoles.

Scheme 7



Based on the above-described two mechanisms of dehydration of 4-hydroxy-Δ^2-thiazolines, the optimal reaction conditions can be chosen and the optimal approach to the thiazole synthesis can be designed. Since the spontaneous thiazole synthesis involves the formation of 2-(R_1R_2C=)- and 2-(RN=)-4-phenyl-Δ^3-thiazolines, both thioamides containing the 2-RCH_2(2-R_2CH) substituents and thioureas can be spontaneously transformed into thiazoles in the Hantzsch reactions with α-haloketones having various structures under the standard conditions. To the contrary, the spontaneous thiazole synthesis is impossible using the reactions of thioamides of aromatic or heteroaromatic acids or thioacetamide, on the one hand, with α-haloketones containing electron-withdrawing α′-substituents or bromoindoxyl-type cyclic α-haloketones, on the other hand. In the latter case, thiazoles can be synthesized only in two steps.[1] If an acidic medium impedes the dehydration of intermediates (4-hydroxy-Δ^2-thiazolines or their cyclic analogs), it is expedient to perform this step under basic catalysis.

To summarize, the proposed mechanism provides an explanation for the empirical data on the difference in the reactivities of thioamides and α-haloketones, which have remained unexplained in terms of the commonly accepted mechanism of the Hantzsch reaction. The results of the present study ensure the prerequisites for broadening the scope of this reaction. Stable methylene bases, *viz*., 2-R-methylene-Δ^3-thiazolines, described in the present study are of interest for the synthesis of thiazoles functionalized at position 2. In addition, these compounds can find application as sensitizers, dyes, and fluorescent labels for biomolecules.[15,16]

Experimental

The elemental analysis for C, H, N, S was carried out on an EA-1108 analyzer (CHNS/O, TDK detector). The NMR spectra were measured on a Varian Unity+400 spectrometer (400 MHz for ^{1}H and 100.6 MHz for ^{13}C) in DMSO-d_6 or $CDCl_3$ using the signal of the residual protons of the solvent (δ 2.49) and the signal of the carbon atoms of the solvent (δ 39.6 and 76.9) as the internal standard for the ^{1}H NMR and ^{13}C NMR spectra, respectively. The deuterium exchange in 2-methyl- and 2-benzyl-4-hydroxythiazolines **1a,b,e** and in the dehydration products of the latter, *viz*., thiazoles **2a,b,e**, was studied by ^{1}H NMR spectroscopy at 20 °C in a DMSO-d_6—CD_3OD solution (1 : 5, v/v, in the case of hydrobromide **1e**) and in DMSO-d_6 with the addition of a CD_3OD—D_2O—DCl mixture (in the case of hydroxythiazolines **1a,b** and thiazoles **2a,b,e**). The water content in the solvents was at most 0.5%. The transformations of hydroxythiazolines **1a,b** were monitored in DMSO-d_6 with the addition of a 3 : 2 : 1 CD_3OD—D_2O—DCl mixture (1/3 v/v). The mass spectra were obtained on a Finnigan SSQ-710 instrument using the direct injection of samples into the ion source (the ionizing electron energy was 70 eV, the temperature of the ionization chamber was 150 °C, samples were heated to 350 °C, the heating rate was 163 deg min^{-1}). The percentage of thiazoles **2b**, **2b(D1)**, and **2b(D2)** was calculated based on the mass spectrometric data taking into account the intensities of the peaks for each of these thiazoles.[17] The IR spectra were recorded on a Perkin—Elmer 457 instrument (Nujol mulls). The calculations for cations **8a—c** and **10a—c** were carried out by the DFT method

with the use of the PBE exchange-correlation potential.[18] The total energies were calculated both with and without the zero-point energy correction. The triple-zeta (TZ) basis set was used for the sulfur atom, and the double-zeta (DZ) basis set was used for all other atoms.[19] The character of stationary points was estimated from the number of negative eigenvalues of the Gaussian. The calculations were performed with the use of the PRIRODA program (version 1.10).[20] The course of the reactions and the purity of the compounds were monitored by TLC on Silufol UV-254 plates (before chromatography of compounds **4b,f,g**, the plates were kept in Et_3N vapor for 3 min) using a 20 : 1 : 3 chloroform—acetone—hexane mixture as the eluent; the visualization was carried out with UV light and iodine vapor. The melting points and the results of IR spectroscopy, mass spectrometry, and ^1H NMR spectroscopy for compounds **2a—g** are consistent with those published earlier.[1,21] The starting thiazolines **1a—g** were synthesized according to a known procedure.[1]

2-Benzyl-4-trifluoromethylthiazole (2c). A mixture of Δ^2-hydroxythiazoline **1c** (1.31 g, 5 mmol) and concentrated (d = 1.18 g cm^{-1}) HCl (0.45 mL, 5 mmol) in Pr^{i}OH (15 mL) was refluxed for 1 min. Aqueous NH_3 was added to the reaction mixture to pH = 8. The reaction solution was cooled and concentrated *in vacuo*. A 2 : 1 petroleum ether—Et_2O mixture (30 mL) was added to the residue. Unconsumed Δ^2-hydroxythiazoline **1c** was filtered off, the solvent was removed *in vacuo*, and water (10 mL) was added to the residue. The crystals that precipitated were filtered off and washed with water. Compound **2c** was obtained in a yield of 0.35 g (29%).[1]

2-Methyl-4-phenylthiazole (2a). A mixture of Δ^2-hydroxythiazoline **1a** (1.93 g, 10 mmol) and concentrated (d = 1.18 g mL^{-1}) HCl (0.90 mL, 10 mmol) in Pr^{i}OH (20 mL) was refluxed for 20 min. Aqueous NH_3 was added to the reaction mixture to pH = 8, and the reaction solution was cooled and concentrated *in vacuo*. The residue was recrystallized from aqueous ethanol (1 : 1). Compound **2a** was obtained in a yield of 1.35 g (77%).[21]

4-Phenyl-2-(R^1R^2C)-Δ^3-thiazolines 4b,f,g. Method *A*. Acetic acid (0.30 g, 5 mmol) was added to a solution of the corresponding Δ^2-hydroxythiazoline **1b,f,g** (5 mmol) in dioxane (30 mL) at 20 °C. After 12 h, the solvent was removed *in vacuo*, and Pr^{i}OH (10 mL) was added to the residue. The crystals that formed were filtered off and washed with aqueous Pr^{i}OH (1 : 1) and water. Acetone was used for recrystallization of compound **4b**; Pr^{i}OH, for compounds **4f,g** (see Table 1).

Method *B*. Triethylamine (1.01 g, 10 mmol) and phenacyl bromide (1.99 g, 10 mmol) were successively added to a solution of thioamide of phenylacetic acid (1.51 g, 10 mmol) in acetone (20 mL) at 20 °C. After 8 h, water (10 mL) was added to the reaction mixture, and the crystals that formed were filtered off, washed with aqueous acetone (1 : 1) and water, and recrystallized from acetone. Compound **4b** was obtained in a yield of 1.68 g (67%).* ^{13}C NMR ($CDCl_3$), δ: 155.39 (s, C(2)); 168.69 (s, C(4)); 44.28 (t, C(5), $^1J_{C,H}$ = 143.5 Hz); 119.77 (d, 2-CH, $^1J_{C,H}$ = 158.2 Hz); 136.26 (s, C(1′)); 132.95 (s, C(1″));** 128.66 ($^1J_{C,H}$ = 161.0 Hz); 128.41 ($^1J_{C,H}$ = 161.0 Hz); 127.95 ($^1J_{C,H}$ = 160.0 Hz); 127.93 ($^1J_{C,H}$ = 159.5 Hz): (d, C(2′), C(6′));** (d, C(3′), C(5′));* (d, C(2″), C(6″));* (d, C(3″), C(5″));* 131.36 ($^1J_{C,H}$ = 161.4 Hz); 126.49 ($^1J_{C,H}$ = 162.5 Hz): (d, C(4′));* (d, C(4″)).*

Method *C*. Triethylamine hydrochloride (1.10 g, 10 mmol) was added to acetone (20 mL). The suspension was refluxed for 10 min and cooled to 20 °C. Compound **1b** (2.69 g, 10 mmol) was added to the reaction mixture. The mixture was stirred at 20 °C for 12 h and diluted with water (10 mL). The product was isolated and purified according to the method *B*. Compound **4b** was obtained in a yield of 1.51 g (60%).

4-R^1-2-R^3-Thiazoles 2b,f,g (general procedure). A solution of HCl (d = 1.18 g cm^{-1}; 0.9 mL, 10 mmol) in Pr^{i}OH (7 mL) was added to a boiling solution of the corresponding Δ^3-thiazoline **4b,f,g** (10 mmol) in Pr^{i}OH (50 mL). The reaction solution was refluxed for 1 min, neutralized with aqueous NH_3 to pH = 8, and concentrated *in vacuo*. The residue was recrystallized from aqueous Pr^{i}OH. The yields of compounds **2b**, **2f**, and **2g** (see Ref. 1) were 2.38 g (95%), 2.61 g (90%), and 3.01 g (92%), respectively.

Thiazoles 2b, **2b(D1)**, and **2b(D2).**** A solution of 6.1 *M* DCl (0.36 r 2.42 mmol) in D_2O was added to a 9 : 1 C_2H_5OD—C_2H_5OH mixture (7 mL). The reaction solution was heated to 75 °C, and then Δ^2-hydroxythiazoline **1b** (0.65 g, 2.42 mmol) was added. The reaction mixture was refluxed for 40 s, neutralized with aqueous NH_3 to pH = 8, and concentrated *in vacuo*. Water (10 mL) was added to the residue. The crystals were filtered off and washed with water. A mixture of compounds **2b**, **2b(D1)**, and **2b(D2)** was obtained in a yield of 0.57 g (93%) (see Table 2). ^1H NMR (DMSO-d_6), δ, a mixture of thiazoles **2b**, **2b(D1)**, and **2b(D2)**: 4.382 (s, 2 H, 2-CH_2, **2b**); 4.363 (s, 1 H, 2-CHD, **2b(D1)**); 7.93 (s, 1 H, H(5), **2b**, **2b(D1)**, **2b(D2)**); 7.97 (m, 2 H, H(2″), H(6″), **2b**, **2b(D1)**, **2b(D2)**); 7.25—7.45 (m, 8 H, H(2′)—H(6′), H(3″)—H(5″), **2b**, **2b(D1)**, **2b(D2)**). ^{13}C NMR (DMSO-d_6), δ, a mixture of thiazoles **2b**, **2b(D1)**, and **2b(D2)**: 169.980 (s, C(2), **2b**); 169.942 (s, C(2), **2b(D1)**); 169.904 (s, C(2), **2b(D2)**); 154.1 (s, C(4), **2b**, **2b(D1)**, **2b(D2)**); 138.132 (s, C(1′), **2b**); 138.100 (s, C(1′), **2b(D1)**); 138.067 (s, C(1′), **2b(D2)**); 134.2 (s, C(1″), **2b**, **2b(D1)**, **2b(D2)**); 129.0 (d, C(2′), C(6′), $^1J_{C,H}$ = 158.5 Hz, **2b**, **2b(D1)**, **2b(D2)**); 128.7[a] (d, C(3′), C(5′), $^1J_{C,H}$ = 160.0 Hz, **2b**, **2b(D1)**, **2b(D2)**); 128.8[a] (d, C(3″), C(5″), $^1J_{C,H}$ = 160.0 Hz, **2b**, **2b(D1)**, **2b(D2)**); 126.9[b] (d, C(4′), $^1J_{C,H}$ = 161.0 Hz, **2b**, **2b(D1)**, **2b(D2)**); 127.9[b] (d, C(4″), $^1J_{C,H}$ = 161.0 Hz, **2b**, **2b(D1)**, **2b(D2)**); 126.1 (d, C(2″), C(6″), $^1J_{C,H}$ = 160.0 Hz, **2b**, **2b(D1)**, **2b(D2)**); 114.2 (d, C(5), $^1J_{C,H}$ = 189.0 Hz, **2b**, **2b(D1)**, **2b(D2)**); 38.811 (t, 2-CH_2, $^1J_{C,H}$ = 129.7 Hz, **2b**); 38.500 (t, 2-CHD, $^1J_{C,D}$ = 19.8 Hz, **2b(D1)**)[c].

A mixture of compounds **2b**, **2b(D1)**, and **2b(D2)** was synthesized analogously in a yield of 0.58 g (95%) (see Table 2) by the reaction of 6.1 *M* DCl (0.36 g, 2.42 mmol) with Δ^3-thiazoline **4b** (0.61 g, 2.42 mmol) in a 9 : 1 C_2H_5OD—C_2H_5OH mixture (7 mL).

* The atomic numbering scheme for compound **4b** is identical to that for compound **2b** (see Scheme 1).

** The group of signals belongs to a group of atoms.

* The group of signals belongs to a group of atoms.

** The atomic numbering scheme for compounds **2b(D1)** and **2b(D2)** is identical to that for compound **2b** (see Scheme 1).

[a,b] The inverse assignment of the signals denoted by the same letters is possible.

[c] The multiplicities and the spin-spin coupling constants in the spectrum measured with full proton spin-spin decoupling.

Crystals of **4b** ($C_{16}H_{13}NS$) are monoclinic at 100 K, space group $P2_1$, a = 7.5834(18), b = 5.7045(13), c = 28.288(8) Å, β = 91.987(7)°, V = 1223.0(5) Å^3, Z = 4, d_{calc} = 1.365 g cm^{-3}, μ(Mo-Kα) = 2.43 cm^{-1}, $F(000)$ = 528. The intensities of 6048 reflections were measured at 100 K on a Smart APEX CCD diffractometer (λ(Mo-Kα) = 0.71072 Å, ω-scanning technique, $2\theta < 54°$); 4018 independent reflections were used in the refinement. The experimental data were processed and merged, and the absorption correction was applied with the use of the SAINT Plus complex program[22] and the SADABS program.[23]

The structure was solved by direct methods using successive electron density maps. The hydrogen atoms were placed geometrically. An analysis of the Fourier maps showed that one of independent molecules in the crystal structure is disordered as a result of a superposition of two identical Z isomers, which are related by a pseudocenter of symmetry lying on the N(3)—C(4) bond). The refined occupancies for two positions of the molecule are 0.4 and 0.6, the carbon atoms of the phenyl rings coinciding for both positions. Both the analysis of the reciprocal lattice and an attempt to perform the refinement with consideration for the possible twinning did not allow the change of the space group to exclude the disorder of the molecule.

The refinement was carried out based on F^2_{hkl} with anisotropic displacement parameters for nonhydrogen atoms and isotropic displacement parameters for hydrogen atoms. The final R factors for the structure of **4b** were R_1 = 0.0795 (calculated based on F_{hkl} for 2516 reflections with $I > 2\sigma(I)$) and wR_2 = 0.2314 (calculated based on F^2_{hkl} for all 4018 reflections), the number of variables was 428, GOF = 1.001. All calculations were performed with the use of the SHELXTL 5.10 program package.[24]

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