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The cyclopropyliminium rearrangement of cyclopropylthiazoles

Yury V. Tomilov,* Rinat F. Salikov, Dmitry N. Platonov, Dmitry L. Lipilin and Aleksandr E. Frumkin

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 6390; e-mail: tom@ioc.ac.ru

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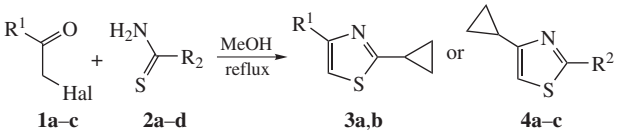
2-Cyclopropylthiazole hydrobromides undergo iminocyclopropane-pyrroline rearrangement in a melt to give the corresponding fused heterocycles, *viz.* 6,7-dihydro-5*H*-pyrrolo[2,1-*b*]thiazol-4-ium bromides. 2-Alkyl- and 2-aryl-4-cyclopropylthiazoles transform into analogous fused heterocycles as hydroiodides and noticeably longer.

We have previously shown[1] that 2-cyclopropylbenzazoles demonstrate similar reactivity of a cyclopropyl moiety as cyclopropylketimines[2–4] and cyclopropanethiomethylimidates[5] and can undergo rearrangement into condensed 2,3-dihydro-1*H*-benzopyrroloazoles under acid nucleophilic catalysis conditions. Similar reaction was observed for the isoquinoline derivative.[6] Reactivity of these azoles increases in the series of cyclopropyl-substituted benzimidazole, benzothiazole and benzoxazole, and the reaction even involves oxazole ring opening in the case of benzoxazole.[1] To study the method that we suggest for synthesizing condensed azoles, it was important to determine whether the absence of a stabilizing benzene ring in the substrate is critical in the rearrangement of 2-cyclopropylthiazoles. Of some interest is also the possibility of rearrangement of 4-cyclopropylthiazoles that do not contain a cyclopropyliminium moiety in explicit form. However, only one example of a similar rearrangement of 2-amino-4-cyclopropylthiazinium bromide on melting (~200 °C) into 3-amino-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]thiazolium bromide was reported so far.[7] Formation of the same fused heterocyclic system was also observed in the reaction of 2-bromo-1-cyclopropylethanone with 2-cyano-3-hetarylprop-2-enethioamides in DMF at 20 °C.[8] The mechanism of this process is not clear, but formation and isomerisation of intermediate 4-cyclopropylthiazoles seems unlikely as the reaction conditions are very mild.

Aside from higher reactivity, the main specific feature of the rearrangement of 2-cyclopropylbenzothiazole in comparison with that of 2-cyclopropylbenzimidazole is that its rearrangement product is a salt-like compound which cannot be easily deprotonated. This feature allows this moiety to be efficiently used as a building block to create pharmacologically active compounds, since the positively charged thiazolium fragment should favour a better solubility in water. In some publications,[9,10] the possibility of using thiazolium salts as prodrugs for malaria treatment was demonstrated. The thiazolyl moiety in these compounds is activated inside the organism to form the active moiety of the drug. Note that compounds with a dihydropyrrolothiazole moiety have not been studied for bioactivity because of their limited availability. The method we propose has a number of advantages over the methods described before.[11]

In order to study the cyclopropyliminium rearrangement in thiazole series, we used the Hantzsch reaction to synthesize a set of cyclopropylthiazoles† from α-halo ketones **1a–c** and thioamides **2a–d** to give both 2-cyclopropylthiazoles **3a**,**b** and 4-cyclopropyl-substituted thiazoles **4a–c**[12] (Scheme 1).

Similarly to the reaction of 2-cyclopropylbenzothiazole,[1] 2-cyclopropylthiazole hydrobromides **3a**,**b** undergo rearrangement in a melt to afford 6,7-dihydro-5*H*-pyrrolo[2,1-*b*]thiazol-4-ium bromides **5a**,**b** in 69 and 85% yields, respectively (Scheme 2).‡



1a–c **2a–d** **3a**,**b** **4a–c**

Ketone	Thioamide	Product	Yield (%)
1a R^1 = Me, Hal = Cl	**2a** R^2 = *c*-C_3H_5	**3a**	83
1b R^1 = Ph, Hal = Cl	**2a** R^2 = *c*-C_3H_5	**3b**	90
1c R^1 = *c*-C_3H_5, Hal = Br	**2b** R^2 = Me	**4a**	67
1c R^1 = *c*-C_3H_5, Hal = Br	**2c** R^2 = Ph	**4b**	95
1c R^1 = *c*-C_3H_5, Hal = Br	**2d** R^2 = pyridin-4-yl	**4c**	62

Scheme 1

In this case, complete conversion of the starting cyclopropylthiazoles is observed in 30 min.

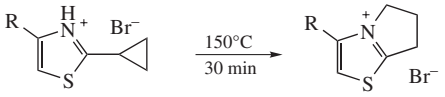
The rearrangement of 4-cyclopropylthiazolium hydrobromides **4a**,**b** that are isomeric to compounds **3a**,**b** occurs extremely slowly at 150 °C in comparison with that of 2-cyclopropylthiazoles, which may be due to the absence of a cyclopropyliminium moiety in explicit form. Still, we attempted to enhance the reactivity of compounds **4a**,**b** and performed a rearrangement of their hydroiodides since hydroiodides rearrange much

† *Synthesis of cyclopropylthiazoles.* A solution of halo ketone **1a–c** (27 mmol) and thioamide (27 mmol) in 100 ml of methanol was heated to reflux for 2 h for bromo ketones or 10 h for chloro ketones. The solvent was removed *in vacuo*, the residue was treated with 100 ml of saturated $NaHCO_3$ solution and extracted with chloroform (3×70 ml). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give the crude product, which was additionally purified by flash column chromatography.

2-Cyclopropyl-4-phenylthiazole **3b**. IR ($CHCl_3$, ν/cm^{-1}): 3112, 3064, 3024, 3004, 1688, 1652, 1600. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.10–1.20 (m, 4H, CH_2CH_2), 2.38 (m, 1H, CH), 7.22 (s, 1H, H^5), 7.36 and 7.90 (2m, 3+2H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 11.1 (CH_2CH_2), 14.7 (CH), 110.3 (C^5), 126.3 and 128.7 (*o*- and *m*-CH), 127.9 (*p*-CH), 133.8 (*i*-C), 154.8 (C^4), 173.5 (C^2). EI MS, *m*/*z*: 201 (82) $[M]^+$, 200 (66) $[M-H]^+$, 175 (32), 134 (100). Found (%): C, 71.69; H, 5.48; N, 6.90. Calc. for $C_{12}H_{11}NS$ (%): C, 71.60; H, 5.51; N, 6.96.

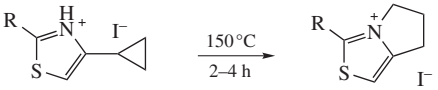
4-Cyclopropyl-2-(pyridin-4-yl)thiazole **4c**. IR ($CHCl_3$, ν/cm^{-1}): 3406, 3085, 3033, 3009, 1597, 1518, 1410. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.99 (m, 4H, CH_2CH_2), 2.10 (m, 1H, CH), 6.95 (s, 1H, H^5), 7.77 (d, 2H, $H^{3'}$, $H^{5'}$, *J* 6 Hz), 8.68 (d, 2H, $H^{2'}$, $H^{6'}$, *J* 6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 8.4 (CH_2CH_2), 12.3 (CH), 112.7 (C^5), 120.2 ($C^{3'}$, $C^{5'}$), 140.7 ($C^{4'}$), 150.3 ($C^{2'}$, $C^{6'}$), 161.0 and 164.1 (C^2 and C^4). EI MS, *m*/*z*: 202 (100) $[M]^+$, 201 (78) $[M-H]^+$, 122 (34), 97 (85). Found (%): C, 65.22; H, 5.51; N, 13.91. Calc. for $C_{11}H_{10}N_2S$ (%): C, 65.32; H, 4.98; N, 13.85.

For characteristics of compounds **3a**,[15] **4a**[12] and **4b**, see Online Supplementary Materials.



3a,**b**·HBr **a** R = Me **5a** (69%)
b R = Ph **5b** (85%)

Scheme 2



4a,**b**·HI **a** R = Me **6a** (58%)
b R = Ph **6b** (68%)

Scheme 3

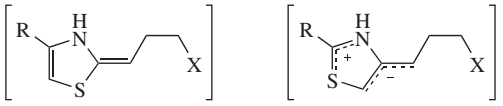
more readily than the corresponding hydrobromides.[1] In fact, hydroiodides **4a**,**b** on heating at 150 °C[§] for a longer time (2–4 h) undergo isomerization with opening of the cyclopropane ring, by analogy with the cyclopropyliminium rearrangement, to produce the corresponding thiazolium iodides **6a**,**b** in 58 and 68% yields, respectively (Scheme 3).

Heating of dihydroiodide **4c** at 150 °C for 2 h leads to complete conversion of the starting cyclopropylthiazole, but a hardly identifiable mixture of compounds is formed. The low selectivity of this reaction is probably owing to the rather high nucleophilicity of the pyridine ring resulting in intermoleculer alkylation or dehydrohalogenation of the intermediate to give oligomeric products in both cases.

The observed difference in the reactivity of 2- and 4-cyclopropylthiazoles results from the large difference in the transition state energies when the cyclopropane ring is opened by a halide ion. The small ring opening stage is highly endothermal (largely due to violation of the thiazole ring aromaticity during this process), hence, owing to Hammond's postulate, the energies and structures of the transition states in the rearrangement of 2- and 4-cyclopropylthiazoles would be similar to the energies and structures of corresponding intermediates **7** and **8**. Obviously, intermediate **7** should be more stable than zwitter-ionic intermediate **8**.

Using known techniques, we also synthesized 5-cyclopropyltetrazole[13] and 5-methyl-3-cyclopropyl-1,2,4-oxadiazole.[14] However, their hydrobromides underwent full conversion at 100–150 °C to yield complex mixture of products.

Thus, similarly to 2-cyclopropylbenzimidazolium and benzothiazolium hydrohalides (unlike cyclopropyloxadiazolium and tetrazolium hydrohalides), 2-cyclopropylthiazolium hydrobromides **3a**,**b** and 4-cyclopropylthiazolium hydroiodides **4a**,**b** can undergo a rearrangement *via* a mechanism similar to that of cyclopropyliminium rearrangement to form the corresponding dihydropyrrolothiazolium salts **5a**,**b** and **6a**,**b**. The rearrangement of 4-cyclopropylthiazoles occurs, despite the formal lack of a cyclopropyliminium moiety, but under more drastic conditions (hydroiodides and longer heating at 150 °C are required).



7 **8**

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.01.007.

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‡ *General procedure for the rearrangement of 2-cyclopropylthiazoles* **3a**,**b**. Hydrobromic acid (1.1 equiv., 48% in water) was added to a solution of 2-cyclopropylthiazole **3a** or **3b** in methanol, the reaction mixture was stirred for 10 min and the solvent was removed *in vacuo*. The residue was heated at 150 °C for 30 min to give the crude thiazolium bromide **5a** or **5b**. The products obtained were purified by recrystallization from propan-2-ol.

*3-Methyl-6,7-dihydro-5*H*-pyrrolo[2,1-*b*]thiazol-4-ium bromide* **5a**:[16] mp 197–200 °C. IR (KBr, ν/cm^{-1}): 3040, 2968, 2884, 1576, 1428. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.45 (s, 3H, Me), 2.69 (m, 2H, H_2C^6), 3.50 (t, 2H, H_2C^7, J 7.5 Hz), 4.46 (t, 2H, H_2C^5, J 7.6 Hz), 7.81 (s, 1H, H^2). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 12.1 (Me), 25.1 (C^6), 30.5 (C^7), 51.0 (C^5) 122.5 (C^2), 139.5 (C^3), 175.1 (C^{7a}). EI MS, *m*/*z*: 140 (53) $[M-Br]^+$, 139 (100) $[M-H]^+$, 113 (69). Found (%): C, 38.13; H, 4.63; N, 6.29. Calc. for $C_7H_{10}BrNS$ (%): C, 38.19; H, 4.58; N, 6.36.

For characteristics of compound **5b**,[17] see Online Supplementary Materials.

§ *General procedure for the rearrangement of 4-cyclopropylthiazoles* **4a–c**. Hydroiodic acid (1.1 equiv. for **4a** and **4b** or 2.1 equiv. for **4c**, 57% in water) was added to a solution of 4-cyclopropylthiazoles **4a–c** in methanol, the reaction mixture was stirred for 10 min and the solvent was removed *in vacuo*. The residue was heated at 150 °C for 2–4 h to give the crude thiazolium iodides **6a** or **6b**. The products were purified by recrystallization from either propan-2-ol (**6a**) or ethanol (**6b**). Rearrangement of **4c** gives a hardly identifiable mixture of products.

*3-Methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]thiazol-4-ium iodide* **6a**: heating for 2 h, mp 192–194 °C. IR (KBr, ν/cm^{-1}): 3039, 2885, 1575, 1427. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.64 (m, 2H, H_2C^6), 2.88 (s, 3H, Me), 3.06 (t, 2H, H_2C^7, J 7.3 Hz), 4.36 (t, 2H, H_2C^5, J 7.4 Hz), 7.69 (s, 1H, H^1). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 15.0 (Me), 24.7 (C^6), 27.1 (C^7), 49.9 (C^5), 112.8 (C^1), 151.3 (C^{7a}), 165.4 (C^3). EI MS, *m*/*z*: 267 (12) $[M]^+$, 140 (65) $[M-I]^+$, 128 (100), 113 (100). Found (%): C, 31.49; H, 3.90; N, 5.20. Calc. for $C_7H_{10}INS$ (%): C, 31.47; H, 3.77; N, 5.24.

For characteristics of compound **6b**, see Online Supplementary Materials.