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UNEXPECTED DIRECTION OF IODOCYCLIZATION OF 3-ALLYLTHIO-5-PHENYL-4H-1,2,4-TRIAZOLE

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The reaction of 3-allylthio-5-phenyl-4H-1,2,4-triazole with iodine to give a mixture of 5,6-dihydro-5-iodomethyl-3-phenyl[1,3]thiazolo[2,3-c][1,2,4]triazole, 6,7-dihydro-6-iodo-3-phenyl-5H-[1,2,4]triazolo-[3,4-b][1.3]thiazine, 5,6-dihydro-6-iodomethyl-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole, and 6,7-dihydro-6-iodo-2-phenyl-5H-[1,2,4]triazolo[5,1-b][1,3]thiazine has been studied. The structure of the products obtained was established using ^{1}H NMR spectroscopy of their dehydriodination products.

Keywords: 3-allylthio-5-phenyl-4H-1,2,4-triazole, 5,6-dihydro-5-iodomethyl-3-phenyl[1,3]thiazolo-[2,3-*c*][1,2,4]triazole, 6,7-dihydro-6-iodo-3-phenyl-5H-[1,2,4]triazolo[3,4-*b*][1,3]thiazine, 5,6-dihydro-6-iodomethyl-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole, 6,7-dihydro-6-iodo-2-phenyl-5H-[1,2,4]triazolo-[5,1-*b*][1,3]thiazine.

The electrophilic cyclization of S-alkynyl [1-3] and S-allenyl [3] derivatives of 5-phenyl-4H-1,2,4-triazole-3-thiol under action of acids and mercury salts has been reported. The authors [1, 3] report the formation of only one regioisomer which is the product of cyclization at the $N_{(2)}$ atom whereas the authors of [2] observe the formation of two isomers simultaneously, the ratio of which is determined by the reaction conditions.

We have studied for the first time the electrophilic iodocyclization of 3-allylthio-5-phenyl-4H-1,2,4-triazole (**1**) in the presence of iodine. Compound **1** was prepared by the reaction of 5-phenyl-4H-1,2,4-triazole-3-thiol with allyl bromide in aqueous NaOH solution at 5-7°C. The iodocyclization was carried out in dichloromethane at room temperature over several days. It was found (see scheme) that not only the two expected five-membered cyclization products – 5,6-dihydro-5-iodomethyl-3-phenyl[1,3]thiazolo[2,3-*c*][1,2,4]-triazole (**3**) and 5,6-dihydro-6-iodomethyl-2-phenyl[1,3]thiazolo[3,2-b][1,2,4]triazole (**5**) – were formed but also the six-membered isomeric products 6,7-dihydro-6-iodo-3-phenyl-5H-[1,2,4]triazolo[3,4-b][1,3]thiazine (**2**) and 6,7-dihydro-6-iodo-3-phenyl-5H-[1,2,4]triazolo[3,4-*b*][1,3]thiazine (**4**) were obtained. In the mixture of reaction products thiazine **2** predominated (46%) and this was similar to thiazole **3** (which was present at a level of 30%) in both chromatographic behavior and solubility. The products of cyclization at atom $N_{(2)}$ (compounds **4** and **5**) were formed in smaller amounts (19 and 5% respectively). They are also close in chromatographic behavior and solubility but significantly less polar than the isomers **2** and **3** (Scheme 1).

The structures of thiazoles **3** and **5** were established by the synthesis from them of the products of fission of HI in methanolic KOH solution to give 5-methyl-2-phenyl[1,3]thiazolo[2,3-*c*][1,2,4]triazole (**6**) from isomer **3** and 6-methyl-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole (**7**) from isomer **5**. In both melting point and ^{1}H NMR spectra they were identical to those reported previously [2, 4-6] (Table 1).

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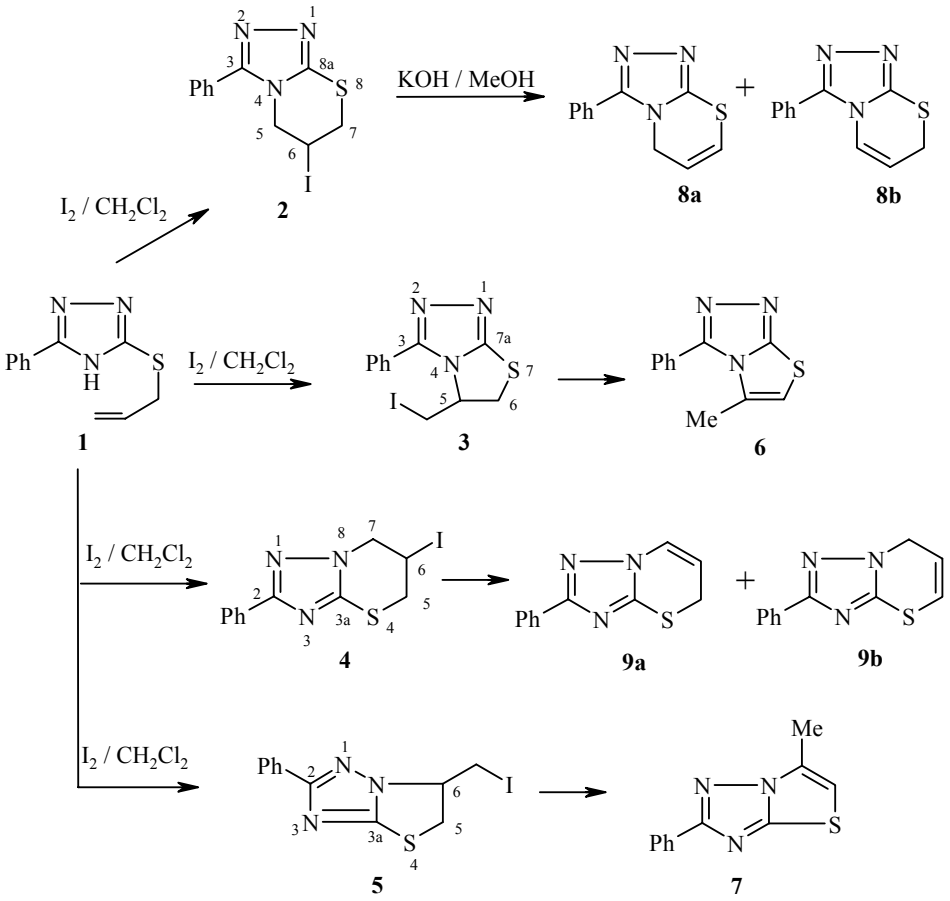
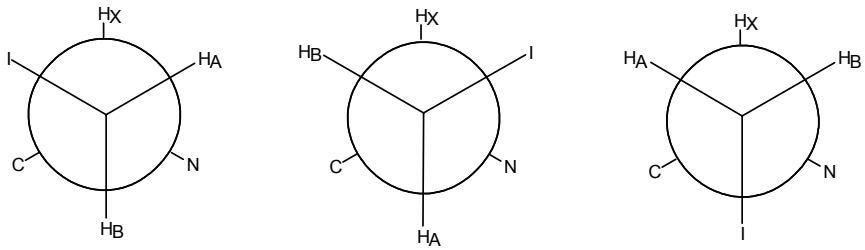
Scheme 1



The ^{1}H NMR spectra of the products of elimination of HI from thiazines **2** and **4** were taken for mixtures of the compounds isomeric by double bond positions in the thiazine ring (**8a,b** and **9a,b** respectively) and were similar to the spectrum of sulfide **1** since they contain a similar vinyl fragment.

The six-membered isomers **2** and **4** show a set of multiplets, the proton spin-spin coupling constants of which were calculated by the known rules for higher order spectra [7]. The SSCC seen in thiazines **2** and **4** between the H-6 proton and the protons of the CH_2N and CH_2S groups point to their existence in a conformation with pseudoequatorial positioning of the iodine atom.

The ^{1}H NMR spectra of the five-membered isomers **3** and **5** showed both signals for the protons of the aromatic ring and an H-5 multiplet in isomer **3** or H-6 in compound **5** together with four quartets for the protons of the thiazole ring and the iodomethyl group. Their spin-spin coupling constants point to a major contribution of the conformers **10a** and **10b** with unsymmetrical positioning of the hydrogen atoms of the iodomethyl group relative to the H_x proton (H-5 in compound **3** and H-6 in compound **5**).



10a **10b** **10c**

TABLE 1. ^{1}H NMR Spectral Characteristics of Compounds **1-9**

Compound	Chemical shifts ($CDCl_3$), δ, ppm (J, Hz)
1	14.4 (1H, s, NH); 7.9-8.1 (2H, m, C_6H_5); 7.4-7.6 (3H, m, C_6H_5); 5.97 (1H, m, –C<u>H</u>=); 5.27 (1H, dt, $^3J_{cis}$ = 15.7, =C<u>H</u>H); 5.09 (1H, dt, $^3J_{trans}$ = 9.9, =CH<u>H</u>); 3.82 (2H, dt, ^4J = 1.3, C<u>H</u>$_2$CH)
2	7.5-7.7 (5H, m, C_6H_5); 4.92 (1H, m, –C<u>H</u>I–); 4.55* (1H, q, $^3J_{MX}$ = 3.7, $^2J_{MN}$ = –13.0, –NCH<u>H</u>$_M$–); 4.45* (1H, q, $^3J_{NX}$ = 8.3, –NC<u>H</u>$_N$H–); 3.61* (1H, q, $^3J_{AX}$ = 2.2, $^2J_{AB}$ = –12.9, –SCH<u>H</u>$_A$I); 3.59* (1H, q, $^3J_{BX}$ = 9.6, –SCH<u>H</u>$_B$I)
3	7.65-7.80 (2H, m, C_6H_5); 7.4-7.5 (3H, m, C_6H_5); 4.99 (1H, m, –NC<u>H</u>–); 4.38 (1H, q, $^4J_{MB}$ = 1.3, $^3J_{MX}$ = 7.3, $^2J_{MN}$ = -11.9, –SCH<u>H</u>$_M$–); 3.82 (1H, q, $^3J_{NX}$ = 1.9, –SC<u>H</u>$_N$H–); 3.36 (1H, q, $^3J_{AX}$ = 10.5, $^2J_{AB}$ = -10.5, –CH<u>H</u>$_A$I); 3.11 (1H, d, $^3J_{BX}$ = 3.0, –CH<u>H</u>$_B$I)
4	7.95-8.05 (2H, m, C_6H_5); 7.35-7.55 (3H, m, C_6H_5); 4.74* (1H, m, –C<u>H</u>I–); 4.81* (1H, dd, $^4J_{MB}$ = 1.6, $^3J_{MX}$ = 5.0, $^2J_{MN}$ = –13.8, –NCH<u>H</u>$_M$–); 4.54 (1H, sext., $^3J_{NX}$ = 9.5, –NC<u>H</u>$_N$H–); 3.67* (1H, dd, $^3J_{AX}$ = 10.6, $^2J_{AB}$ = -12.6, –SCH<u>H</u>$_A$I); 3.55* (1H, d, $^3J_{BX}$ = 3.3, –SCH<u>H</u>$_B$I)
5	8.0–8.1 (2H, m, C_6H_5); 7.4-7.5 (3H, m, C_6H_5); 4.55 (1H, m, –NC<u>H</u>–); 4.16 (1H, q, $^3J_{MX}$ = 8.1, $^2J_{MN}$ = -11.9, –SCH<u>H</u>$_M$–); 3.84 (1H, q, $^3J_{NX}$ = 5.4, –SC<u>H</u>$_N$H–); 3.70 (1H, q, $^3J_{AX}$ = 3.0, $^2J_{AB}$ = -10.6, –CH<u>H</u>$_A$I); 3.51 (1H, q, $^3J_{BX}$ = 9.1, –CH<u>H</u>$_B$I)
6	7.4-7.7 (5H, m, C_6H_5); 6.55 (1H, q, ^4J = 1.3, H-6); 2.12 (3H, d, CH_3)
7	8.1-8.2 (2H, m, C_6H_5); 7.4-7.6 (3H, m, C_6H_5); 6.59 (1H, q, ^4J = 1.2, H-5); 2.58 (3H, d, CH_3)
8a*[2]	7.5-7.7 (5H, m, C_6H_5); 6.41 (1H, dt, ^3J = 10.0, ^4J = 1.7, –SC<u>H</u>=); 5.96 (1H, dt, –C<u>H</u>=); 4.79 (2H, dd, ^3J = 3.7, –NC<u>H</u>$_2$–)
8b*[2]	7.5-7.7 (5H, m, C_6H_5); 6.89 (1H, dt, ^3J = 8.0, ^4J = 1.4, –NC<u>H</u>=); 5.76 (1H, dt, –C<u>H</u>=); 3.61 (2H, dt, ^3J = 5.4, –SC<u>H</u>$_2$–)
9a*[2]	7.4-8.0 (5H, m, C_6H_5); 6.31 (1H, dt, ^3J = 10.0, ^4J = 1.9, –SC<u>H</u>=); 5.99 (1H, dt, –C<u>H</u>=); 5.04 (2H, dd, ^3J = 3.4, –NC<u>H</u>$_2$–)
9b*[2]	7.4-8.0 (5H, m, C_6H_5); 7.10 (1H, dt, ^3J = 8.5, ^4J = 1.5, –NC<u>H</u>=); 5.51 (1H, dt, –C<u>H</u>=); 3.72 (2H, dt, ^3J = 5.3, –SC<u>H</u>$_2$–)

* As part of a multiplet.

*[2] As a mixture of isomers.

The spin-spin coupling constant values are in good agreement with relative stability of conformers for all of the cyclization products **2-5** as determined by a full energy semiempirical PM3 calculation (Table 2). Thus, according to the calculations, the conformers with pseudoequatorial iodine atom have a greater stability in the six-membered products **2** and **4** and in thiazoles **3** and **5** the conformer **10a** is more stable in which the iodine atom is placed out of the plane of the thiazole ring. The calculation also showed that, for thiazole **3**, the conformation **10b** does not overall exist in a potential energy minimum, probably due to the unfavorable steric interaction of the iodine atom with the phenyl group.

TABLE 2. Relative Energy (E) of the Conformers of the Cyclization Products **2-5***

Conformer	E, kJ/mol			
	2	**3**	**4**	**5**
10a	—	31.1	—	36.3
10b	—	Unstable	—	58.4
10c	—	53.7	—	56.7
Axial iodine atom	21.0	—	23.7	—
Equatorial iodine atom	0.0	—	0.1	—

* The energy of the most stable conformer was used as the zero energy value.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker (200 MHz) spectrometer. TLC was carried out on Sorbfil PTSK-V-UV plates and revealed using UV irradiation or iodine vapor.

3-Allylthio-5-phenyl-4H-1,2,4-triazole (1). 5-Phenyl-4H-1,2,4-triazole-3-thiol (10.0 g, 56.4 mmol) and NaOH (3.40 g, 85 mmol) were dissolved in water (200 ml) in a flat-bottomed flask. The solution was cooled to 5-7°C and allyl bromide (5.37 ml, 62.1 mmol) was added dropwise. The mixture was stirred at reduced temperature for 3-4 h, acidified with acetic acid (1.5 ml) to pH 7, and the precipitated sulfide **1** was filtered off, washed with water, and dried. The yield after drying was 11.2 g (91%). Recrystallization from a mixture of benzene (35 ml) and hexane (30 ml) gave 9.97 g of a needle-shaped crystalline product; mp 104°C, R_f 0.29 ($CHCl_3$–acetone, 10:1). Found, %: S 14.7. $C_{11}H_{11}N_3S$. Calculated, %: S 14.8.

5,6-Dihydro-5-iodomethyl-3-phenyl[1,3]thiazolo[2,3-*c*][1,2,4]triazole (3) and 6,7-Dihydro-6-iodo-3-phenyl-5H-[1,2,4]triazolo[3,4-*b*][1,3]thiazine (2); 5,6-Dihydro-6-iodomethyl-2-phenyl[1,3]thiazolo[3,2-*b*]-[1,2,4]triazole (4) and 6,7-Dihydro-6-iodo-2-phenyl-5H-[1,2,4]triazolo[5,1-*b*][1,3]thiazine (5). Sublimed iodine (19.02 g, 75.0 mmol) was added to suspension of compound **1** (6.51 g, 30.0 mmol) in CH_2Cl_2 (200 ml). The mixture was held at room temperature in the dark for several days, then CH_2Cl_2 was distilled off under reduced pressure. The residue was dissolved in acetone (70 ml) and solution of $Na_2S_2O_3·5H_2O$ (27.07 g, 105 mmol) and Na_2CO_3 (3.81 g, 36.0 mmol) in water (300 ml) was added with cooling. The precipitated mixture of cyclization products was separated and dried (9.80 g, 95%). For the separation of the cyclization products **4** and **5** the mixture was treated with benzene (200 ml) at room temperature. The insoluble part (7.15 g, a mixture of **2** and **3**) was recrystallized from 70% acetic acid to give 3.80 g (37% based on sulfide **1**) of thiazine **2**. The mother liquor was evaporated at reduced pressure and suspended in water, the insoluble precipitate after two recrystallizations from ethanol giving 1.93 g (19% based on compound **1**) of thiazole **3**. The benzene extract containing the mixture of isomers **4** and **5** was evaporated and the residue (2.24 g) was chromatographed on alumina column using benzene as eluent to give 0.40 g (4% based on sulfide **1**) of thiazole **5** (fraction I) and 1.50 g (14% based on sulfide **1**) of thiazine **4** (fraction II).

The mixture of isomers **2** and **3** (500 mg) was quantitatively separated on alumina chromatographic column (ethyl acetate as eluent) to give 195 mg (39% based on 500 mg of the mixture of **2** and **3**) of thiazole **3** and 290 mg (58% based on 500 mg of the mixture of **2** and **3**) of thiazine **2**.

The mixture of isomers **4** and **5** (500 mg) was quantitatively separated on the alumina chromatographic column (benzene as eluent) to give 105 mg (21% based on 500 mg of the mixture of **4** and **5**) of thiazole **5** and 388 mg (78% based on 500 mg of the mixture of **4** and **5**) of thiazine **4**.

6,7-Dihydro-6-iodo-3-phenyl-5H-[1,2,4]triazolo[3,4-*b*][1,3]thiazine (2). Mp 194°C (70% AcOH), R_f 0.21 (ethyl acetate). Found, %: I 36.5; S 9.4. $C_{11}H_{10}IN_3S$. Calculated, %: I 37.0. S 9.3.

5,6-Dihydro-5-iodomethyl-3-phenyl[1,3]thiazolo[2,3-*c*][1,2,4]triazole (3). Mp 189°C (ethanol), R_f 0.24 (ethyl acetate). Found, %: I 36.6; S 9.3. $C_{11}H_{10}IN_3S$. Calculated, %: I 37.0; S 9.3.

6,7-Dihydro-6-iodo-2-phenyl-5H-[1,2,4]triazolo[5,1-*b*][1,3]thiazine (4). Mp 138°C (benzene–hexane), R_f 0.32 (ethyl acetate–hexane, 2:3). Found, %: I 36.8; S 9.3. $C_{11}H_{10}IN_3S$. Calculated, %: I 37.0; S 9.3.

5,6-Dihydro-6-iodomethyl-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole (5). Mp 115°C (*i*-PrOH), R_f 0.34 (ethyl acetate–hexane, 2:3). Found, %: I 36.9; S 9.5. $C_{11}H_{10}IN_3S$. Calculated, %: I 37.0; S 9.3.

5-Methyl-3-phenyl[1,3]thiazolo[2,3-*c*][1,2,4]triazole (6). Compound **3** (343 mg, 1.00 mmol) was dissolved in 5% KOH solution in methanol (15 ml), heated to reflux, and left for several hours at room temperature. Methanol was evaporated at reduced pressure, the residue was extracted with chloroform (3 × 10 ml) and the combined extract was dried with anhydrous sodium sulfate and chloroform evaporated. The residue was recrystallized from a mixture of benzene and hexane to give thiazole **6** (118 mg, 55%); mp 150°C (mp 150°C [4]), R_f 0.28 (ethyl acetate).

6-Methyl-2-phenyl[1,3]thiazolo[3,2-*b*][1,2,4]triazole (7) was prepared similarly from compound **5** in 108 mg (50%) yield; mp 125°C (mp 124°C [4]), R_f 0.37 (ethyl acetate–hexane, 2:3).

Mixture of 3-Phenyl-5H-[1,2,4]triazolo[3,4-*b*][1,3]thiazine (8a) and 3-Phenyl-7H-[1,2,4]triazolo-[3,4-*b*][1,3]thiazine (8b). Removal of HI from thiazine **2** (100 mg, 0.29 mmol) was carried out similarly to the preparation of compound **6**. Evaporation of solvent gave 59 mg (95%) of the mixture of the isomers **8a** and **8b**.

Mixture of 2-Phenyl-5H-[1,2,4]triazolo[5,1-*b*][1,3]thiazine (9a) and 2-Phenyl-7H-[1,2,4]triazolo-[5,1-*b*][1,3]thiazine (9b) was prepared similarly from compound **4** in 61 mg (98%) yield.

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