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REGIOSELECTIVITY OF THE MONOHALOGENATION OF 4-ALLYL-3-ALLYLAMINO-1,2,4-TRIAZOLE-5-THIONE

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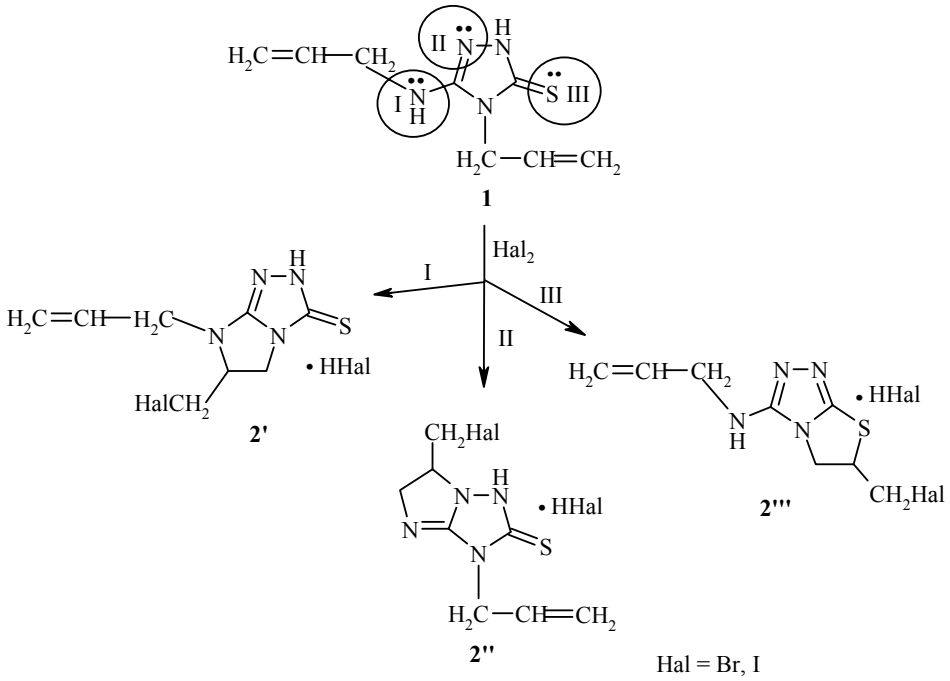
The monohalogenation of 4-allyl-3-allylamino-1,2,4-triazole-5-thione has been studied. It was established that the action of bromine and iodine on 4-allyl-3-allylamino-1,2,4-triazole-5-thione at low temperatures leads to selective closure of a thiazoline ring.

Keywords: 4-allyl-3-allylamino-1,2,4-triazole-5-thione, halogen, [1,3]thiazolo[2,3-*c*][1,2,4]triazole, regioselectivity.

The development of methods of obtaining new condensed heterocyclic compounds from 1,2,4-triazolethiones is an urgent problem, since these compounds possess a broad spectrum of physiological activity as analgetic, vasodilating, anti-inflammatory, and bactericidal agents and show tranquilizing action [1-3]; they are used as highly effective additives to photomaterial [4], and also are inhibitors of corrosion of non-ferrous metals and alloys based on them [5].



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Methods are known for the synthesis of condensed systems from 1,2,4-triazolethiones by heterocyclization of monoallyl-substituted 1,2,4-triazolethiones by the action of halogens [6-10] and mineral acids [10, 11], as a result of which the formation of condensed thiazolotriazoles was noted.

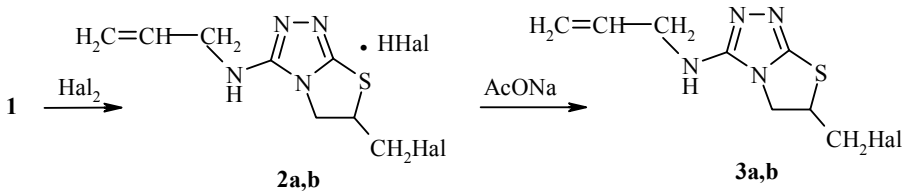
With the aim of studying the relative reactivity of allyl substituents in the triazole ring, and also to obtain condensed triazoles containing unsaturated substituents, we have studied the regioselectivity of monohalogenation of 4-allyl-3-allylamino-1,2,4-triazole-5-thione (**1**) previously obtained by alkaline cyclization of diallyldithiourea [12].

In connection with the fact that triazole **1** contains several nucleophilic centers (I, II, III) with the participation of which electrophilic heterocyclization may occur, it is theoretically possible to form the hydrogen halides of imidazo[2,1-*c*][1,2,4]triazole-3-thione (**2'**), imidazo[2,1-*b*][1,2,4]triazole-3-thione (**2"**), and [1,3]thiazolo[2,3-*c*][1,2,4]triazole **2"'**.

Heterocyclization was effected at a reactant ratio of triazole **1** to halogen of 1 : 1 in various solvents (glacial acetic acid, ethanol, chloroform) and at different temperatures.

After a series of experiments it was noted that monohalogenation of triazole **1** occurs predominantly with the formation of the hydrohalide of thiazolinotriazole **2"'**. We established that maximum selectivity is observed when using chloroform as solvent and carrying out the process at 0-5°C in the case of bromination and on using ethanol at room temperature in the case of iodination.

The immediate halogenation products are the hydrohalides **2**, which may readily be converted into the corresponding thiazolinotriazoles **3** by the action on them of an alcoholic solution of sodium acetate.



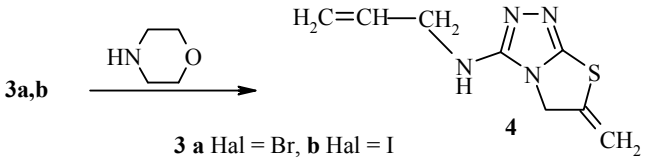
2, 3 a Hal = Br, **b** Hal = I

It was noted that on using a more polar solvent (acetic acid) resinification of the reaction mixture is observed, which leads to a reduction of the selectivity of the process. A mixture is formed of all the theoretically possible structures **2'**, **2",** and **2"'** with **2"'** predominating (confirmed by data of the ^{1}H NMR spectrum of the reaction mixture). An increase in reaction temperature has an analogous effect. On brominating triazole **1** at room temperature resinification of the reaction mixture is also observed.

It is possible to explain the predominance of structure **2"'** by the fact that the π-electron density on the allyl substituent of the π-electron-abundant triazole ring will be higher in comparison with the π-electron density of the allyl substituent on the electron-withdrawing exocyclic nitrogen atom, as a result of which polarization of the halogen (the first step of the classical mechanism of electrophilic heterocyclization [13]) is readily effected by the multiple bond of the substituent in position 4 of the triazole ring. At the following stage closure of just the thiazoline (structure **2"'**) and not the imidazoline (structure **2'**) ring may be explained by the high nucleophilicity of the sulfur atom.

The direction of heterocyclization described by us is also demonstrated by chemical conversion and the dehydrohalogenation of compounds **3** under the action of morpholine.

As a result of the reaction of thiazolinotriazoles **3** with morpholine the same compound **4** is formed, which was confirmed by TLC, by the absence of melting point depression, and by ^{1}H NMR spectra.



Signals were absent from the ^{1}H NMR spectra of condensed thiazinotriazoles **2**, **3** for the protons of two allyl substituents as was the signal (12.67 ppm) of the thioamide proton, characteristic of the initial triazole **1** [12]. In the spectrum signals were displayed for only one allyl substituent and signals characteristic of an ABX spin system, which confirms the closure of the saturated five-membered ring. The absence from the spectra of compounds **2**, **3** of a signal for the thioamide proton and the presence of a signal of the proton of the exocyclic amino group (at 9.28 for **2a**, 6.77 ppm for **3b**) demonstrates absolutely the formation of the thiazoline ring on cyclization of triazole **1**. The ^{1}H NMR spectrum of compound **4** also confirms the correctness of the structures of compounds **2, 3** proposed by us. The signal of the N-CH_2 group protons of the thiazoline ring are displayed as a singlet at 4.71, and the signals of the exocyclic methylene group as two singlets at 5.52 (*trans* proton) and 5.42 ppm (*cis* proton). In the case of the formation of the isomeric [1,3]thiazolo[2,3-*c*][1,2,4]thiazole (described on cyclization of allylthiotriazoles [8, 9]) in the spectrum of the compound obtained by the action of morpholine, the signal of the protons of the S-CH_2 group should have been displayed in a significantly higher field region of the spectrum [14, 15], and on formation of thiazinotriazoles (described in [8, 14, 15]), a picture of a split ABX_2 spin system must be observed.

Conditions have therefore been determined experimentally for the maximum selectivity of halogenation of triazole **1**. It was also noted that the formation of structures [1,3]thiazolo[2,3-*c*][1,2,4]triazole **3** indicate the higher reactivity of the allyl substituent on the triazole heterocycle than the allyl substituent on the exocyclic nitrogen atom.

EXPERIMENTAL

TLC was carried out on Sorbfil plates at 27°C (adsorbent was silica gel; visualization with iodine). ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz), internal standard was TMS.

The method of synthesis of 4-allyl-3-allylamino-1,2,4-triazole-5-thione (**1**) is described in [12].

3-Allylamino-6-bromomethyl-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]triazole Hydrobromide (2a). A solution of bromine (0.27 ml, 0.81 g, 5 mmol) in chloroform (10 ml) was added dropwise to a solution of triazole **1** (1.00 g, 5 mmol) in chloroform (110 ml) with constant stirring and cooling with ice. The reaction mixture was stirred for 2 h at 0-5°C, the solid was filtered off, washed with ether, and recrystallized from ethanol. Yield was 70%; mp 96-98°C (from ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.92 (2H, t, *J* = 3.3, C$\underline{H}_2$CH=CH_2); 3.98 (2H, m, CH_2Br); 4.30 (2H, m, NCH_2-*cyclo*); 4.90 (1H, m, CH-*cyclo*); 5.23 (1H, d, *J* = 10.8, CH_2CH=C$\underline{H}_2$); 5.37 (1H, d, *J* = 17.4, CH_2CH=C$\underline{H}_2$); 5.89 (1H, m, CH_2C$\underline{H}$=CH_2); 9.28 (1H, m, AllylN$\underline{H}$); 13.60 (1H, m, HBr). Found, %: C 26.86; H 3.33; Br 44.29; N 16.04; S 8.86. $C_8H_{12}Br_2N_4S$. Calculated, %: C 26.97; H 3.37; Br 44.94; N 15.73; S 8.99.

3-Allylamino-6-iodomethyl-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]triazole Hydroiodide (2b). A solution of finely powdered iodine (1.27 g, 5 mmol) in ethanol (30 ml) was added in small portions with constant stirring to a solution of triazole **1** (1.00 g, 5 mmol) in ethanol (30 ml). The reaction mixture was left for 48 h at room temperature, the solvent evaporated, the residue was washed with ether, and recrystallized from ethanol. Yield 83%; mp 117-120°C (from ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.58-3.72 (2H, m, CH_2I); 3.85 (2H, t, *J* = 3.3, C$\underline{H}_2$CH=CH_2); 3.92-4.18 (2H, m, NCH_2-*cyclo*); 4.99 (1H, m, CH-*cyclo*); 5.12 (1H, d, *J* = 10.8, CH_2CH=C$\underline{H}_2$); 5.31 (1H, d, *J* = 17.4, CH_2CH=C$\underline{H}_2$); 5.91 (1H, m, CH_2C$\underline{H}$=CH_2); 9.02 (1H, m, AllylN$\underline{H}$); 13.60 (1H, m, HI). Found, %: C 21.54; H 2.72; I 55.12; N 12.59; S 7.26. $C_8H_{12}I_2N_4S$. Calculated, %: C 21.33; H 2.67; I 56.44; N 12.44; S 7.11.

3-Allylamino-6-halomethyl-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]triazole 3 (General Method). Aqueous 5% sodium acetate solution (10 ml, 6 mmol) was added to a solution of salt **2** (3 mmol) in DMSO (10 ml) or in ethanol (30 ml), the mixture was stirred for 1 h at room temperature and then water (50 ml) was added. The solid was filtered off and recrystallized from ethanol.

3-Allylamino-6-bromomethyl-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]triazole (3a). Yield 76%; mp 122-125°C (from ethanol). R_f 0.81 (Sorbfil, ethanol–chloroform–ether, 1:1:3). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.80 (2H, t, *J* = 3.3, C<u>H</u>$_2$CH=CH$_2$); 3.92 (2H, m, CH$_2$Br); 4.12 (2H, m, NCH$_2$-*cyclo*); 4.64 (1H, m, CH-*cyclo*); 5.14 (1H, d, *J* = 10.5, CH$_2$CH=C<u>H</u>$_2$); 5.28 (1H, d, *J* = 17.1, CH$_2$CH=C<u>H</u>$_2$); 5.94 (1H, m, CH$_2$C<u>H</u>=CH$_2$); 6.82 (1H, m, AllylN<u>H</u>). Found, %: C 34.82; H 3.92; Br 29.31; N 20.19; S 11.62. $C_8H_{11}BrN_4S$. Calculated, %: C 34.91; H 4.00; Br 29.09; N 20.36; S 11.64.

3-Allylamino-6-iodomethyl-5,6-dihydro[1,3]thiazolo[2,3-*c*][1,2,4]triazole (3b). Yield 90%; mp 165-168°C (from ethanol). R_f 0.71 (Sorbfil, ethanol–chloroform–ether, 1:1:3). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.46-3.72 (2H, m, CH$_2$I); 3.77 (2H, t, *J* = 3.3, C<u>H</u>$_2$CH=CH$_2$); 3.86-3.95, 4.04-4.16 (2H, 2m, NCH$_2$-*cyclo*); 4.85 (1H, m, CH-*cyclo*); 5.11 (1H, d, *J* = 10.5 , CH$_2$CH=C<u>H</u>$_2$); 5.24 (1H, d, *J* = 17.1, CH$_2$CH=C<u>H</u>$_2$); 5.93 (1H, m, CH$_2$C<u>H</u>=CH$_2$); 6.77 (1H, m, AllylN<u>H</u>). Found, %: C 29.79; H 3.40; I 39.73; N 17.17; S 9.88. $C_8H_{11}IN_4S$. Calculated, %: C 29.81; H 3.42; I 39.44; N 17.39; S 9.94.

3-Allylamino-6-methylene-5,6-dihydro[1,3]thiazolo[2.3-*c*][1,2.4]triazole (4). Morpholine (0.5 ml, 5.7 mmol) was added to a solution of salt **3** (2 mmol) in ethanol (20 ml) and the mixture was heated on a water bath for 2 h. The solid precipitated on cooling was separated, and the filtrate evaporated. The residue, compound **4**, was recrystallized from chloroform. Yield 65%; mp 142-144°C (from ethanol). R_f 0.84 (Sorbfil, ethanol–chloroform–ether, 1:1:3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.96 (2H, t, *J* = 3.3, C<u>H</u>$_2$CH=CH$_2$); 4.71 (2H, s, NCH$_2$-cyclo); 5.17 (1H, d, *J* = 19.2, CH$_2$CH=C<u>H</u>$_2$); 5.28 (1H, d, *J* = 9.6, CH$_2$CH=C<u>H</u>$_2$); 5.30 (1H, m, NH); 5.32 (1H, s, =CH$_2$); 5.42 (1H, s, =CH$_2$); 6.00 (1H, m, CH$_2$C<u>H</u>=CH$_2$). Found, %: C 49.18; H 5.11; N 28.63; S 16.41. $C_8H_{10}N_4S$. Calculated, %: C 49.48; H 5.15; N 28.87; S 16.49.

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