Synthesis and opening of the thiadiazine ring in 6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines

A. A. Kolodina, N. I. Gaponenko, and A. V. Lesin*

South Federal University, Department of Chemistry,
7 ul. Zorge, 344090 Rostov-on-Don, Russian Federation.
Fax: +7 (863) 26 6567. E-mail: lexandra@inbox.ru

A reaction of 3-benzylthiotriazole-4-amines with aromatic aldehydes leads to the formation of 6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines. A dihydrothiadiazine ring opening along the N—N bond occurs by the action of strong bases.

Key words: [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines, dihydrothiadiazine, annulation, ring opening, 2-[(1,2,4-triazol-3-yl)thio]ethanimine, X-ray crystallography.

Earlier,[1] we reported on a new thermoinduced intramolecular cyclization of thiomethylene-active derivatives of *N*-quinoneimino-*o*-aminothiophenols, in the course of which spiroconjugated benzothiazines are formed. The present work is aimed at the study of possibilities of intramolecular cyclization of thiomethylene-active derivatives of aminothiotriazoles, the heterocyclic analogs of *o*-aminothiophenols.

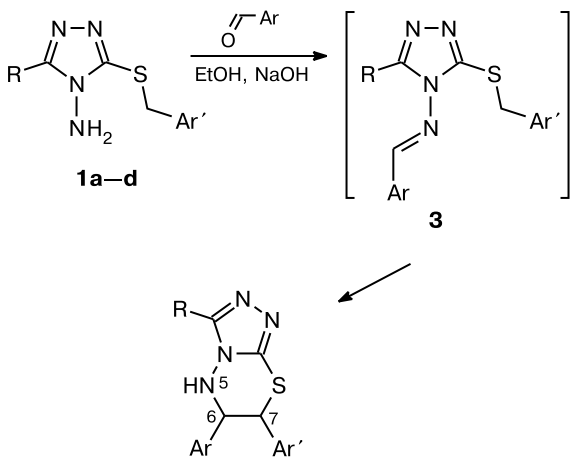
A base-catalyzed condensation of 3-[(4-nitrobenzyl)thio]-5-R-1,2,4-triazol-4-amines **1a—c** with aromatic aldehydes leads to 6,7-dihydro-5*H*-triazolo[3,4-*b*]-[1,3,4]thiadiazines **2**. In the absence of electron-withdrawing NO_2 group in the thiobenzylic fragment, the heterocyclization does not take place and the reaction stops after formation of imine **3** (Scheme 1).

A dependence of the cyclization course on the presence of a base in the reaction medium and on the lability of the thiomethylene protons allows one to suggest that the mechanism of the thiadiazine ring formation includes elimination of the proton of the methylene group activated by the electron-withdrawing substituent followed by the nucleophilic attack of the carbanionic center formed at the C atom of the azomethine group, in the course of which the C(6)—C(7) bond of triazolothiadiazine **2** is formed.

The formation of compounds **2** is confirmed by the transformation of the signals for the methylene and amino groups in the ^{1}H NMR spectrum of the starting compound **1** into the one-proton signals of the vicinal protons of two CH groups and the NH group of the thiadiazine ring. The sharp resolution of the signals for H(6) and H(7) and the value of their spin-spin coupling constants (J = 10 Hz) attest the diastereoselectivity of the process of the thiadiazines **2** formation.

The synthesized dihydro-1,2,4-triazolothiadiazines **2a,b** under the action of strong bases give compounds **4a,b**, which display solvatochromic properties (Scheme 2).

Scheme 1



1: Ar′ = 4-$NO_2C_6H_4$ (**a—c**), Ph (**d**);
R = 3-C_5H_4N (**a**), Ph (**b**), 4-C_5H_4N (**c, d**);
2: Ar′ = 4-$NO_2C_6H_4$ (**a—e**);
R = 3-C_5H_4N (**a**), Ph (**b, c**), 4-C_5H_4N (**d, e**);
Ar = 4-BrC_6H_4 (**a, b, e**), 4-$NO_2C_6H_4$ (**c**), 3-$NO_2C_6H_4$ (**d**);
3: R = 4-C_5H_4N, Ar = 4-BrC_6H_4, Ar′ = Ph

In the mass spectrum of compound **4a**, a peak of the molecular ion is observed, which corresponds to the weight of this compound and the starting triazolothiadiazine **2a**. In the ^{1}H NMR spectra of compounds **4** recorded in deuterochloroform, there are a two-proton singlet at δ 5.2 and a one-proton singlet at δ 11.2. At the same time, when DMSO-d_6 was used as the solvent, two one-proton singlets at δ 6.6 and 6.9 and a one-proton singlet at δ 14.0 can be observed in the spectrum. Signals in

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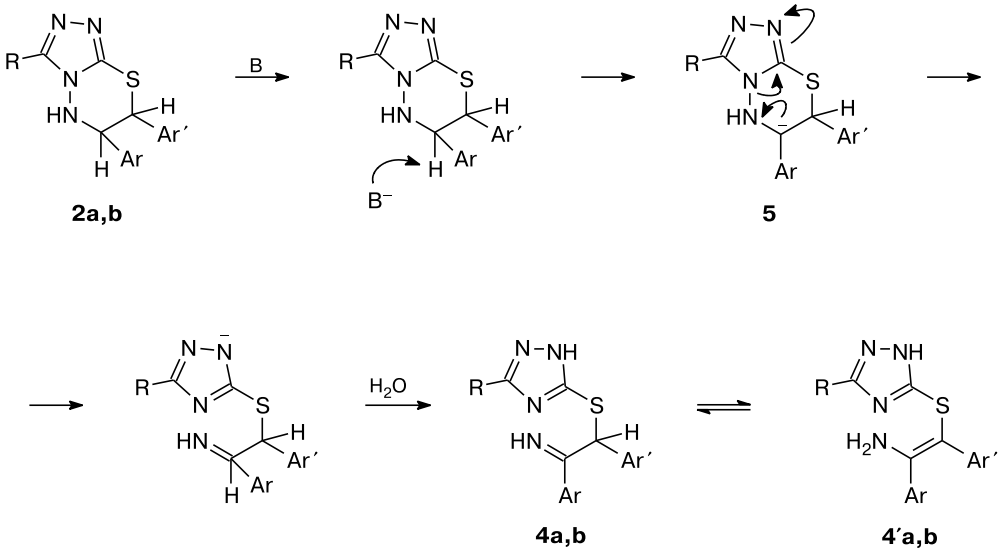
Scheme 2



B is a base

the aromatic region of these spectra attest the presence of 3-pyridyl (phenyl) and both *p*-substituted aromatic rings. Taking into account the spectral data obtained, the two structures **4** and **4′** can be suggested as the most probable, which are isomeric to the molecules of starting triazolothiadiazines **2**. In our view, the solvatochromic properties are caused by the mutual transformations of the amino and imino tautomers in different solvents.

A suggested mechanism of the thiadiazine ring opening includes elimination of the proton H(6) and formation of anion **5** with further stabilization of the negative charge in the triazole ring by the cleavage of the N—N bond.

The X-ray data confirmed the structure of compound **4′a** (Fig. 1).

The pyridine and triazole rings of the molecule **4′a** are in the same plane. In the triazole fragment, the nitrogen atom N(2) of the pyrrole type has virtually the planar configuration (it comes out of the plane of the triazole ring by 0.022 Å). The C(2)=C(1) bond is oriented away from the triazole ring (the torsional angle C(1)—C(2)—S(1)—C(3) is equal to 113.0(5)°), its length is 1.375(7) Å. The *cis*-substituents, *p*-NO_2- and

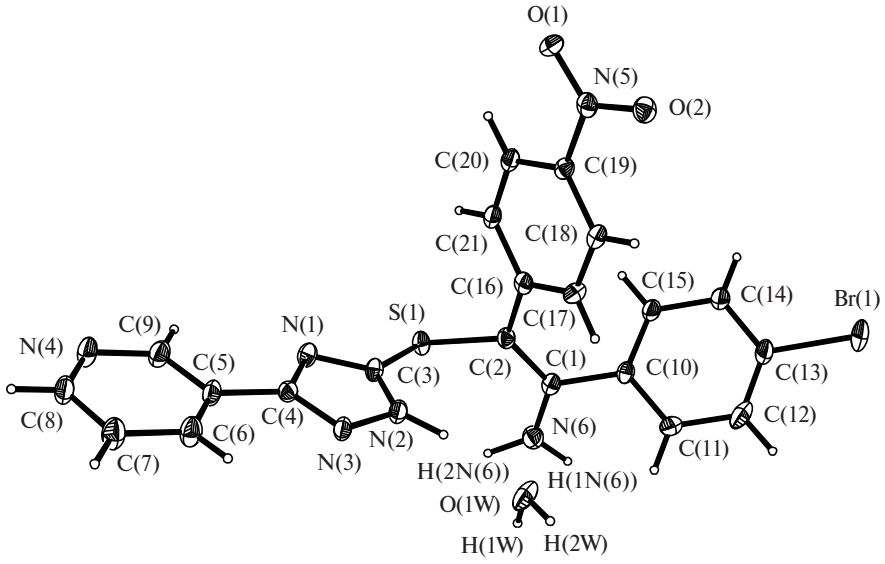


Fig. 1. The X-ray data on the structure of molecule **4′a**.

p-Br-phenyl fragments are turned with respect to the plane of the C(2)=C(1) bond by ~40°: the torsional angle C(2)—C(1)—C(10)—C(15) is equal to 47.0(7)°, whereas the angle C(17)—C(16)—C(2)—C(1) to 38.0(8)°.

In conclusion, we suggested a new method for the annulation of dihydrothiadiazine ring to aminothiotriazoles, a distinguishing feature of which is the formation of the carbon—carbon bond in the final step of the heterocyclization. The triazolothiadiazines that formed by the action of a strong base are able to undergo the opening of the hydrogenated heterocycle along the N—N bond, which leads to triazolylthioethanimines.

Experimental

^{1}H NMR spectra were recorded on a Varian Unity-300 (300 MHz) and Bruker DPX-250 (250 MHz) spectrometers at 25 °C with Me_4Si as the internal standard. Mass spectra were recorded on a Finnigan MAT INCOS 50 instrument.

Monocrystals of compound **4´a** were obtained by crystallization from acetonitrile. The X-ray analysis of compound **4´a** (the experimental set of 2659 reflections) was obtained on a Syntex $P2_1$ diffractometer at 193 K (graphite monochromator, λ(Mo-Kα)-irradiation, $2\theta_{max} = 54°$), the monocrystal size was 0.40×0.25×0.15 mm. When the equivalent reflections were averaged, 2530 independent reflections were obtained (R_{int} = 0.0238), which were used for decoding and refining of the structure. Absorption ($\mu = 20.06$ cm^{-1}) was not considered. The red plate-like crystals $C_{21}H_{17}BrN_6O_3S$, M = 513.38, monoclinic. At 193 K, $a = 10.252(2)$ Å, $b = 10.073(3)$ Å, $c = 10.648(3)$ Å, $\alpha = 90°$, $\beta = 94.335(18)°$, $\gamma = 90°$, $V = 1096.5(5)$ Å^3, the space group $P2(1)$, $Z = 2$, $d_{calc} = 1.555$ g cm^{-3}. The structure was solved by the direct method, all the nonhydrogen atoms were localized in the differential syntheses of electron density and refined on F^2_{hkl} in anisotropic approximation; all the hydrogen atoms were placed into the geometrically calculated positions and considered during refining by the riding model with $U(H) = nU(C)$, where $U(C)$ is the equivalent temperature factor of the C atom, which the corresponding H atom is bonded to, $n = 1.2$ and 1.5 for the carbon atoms C_{sp^2} and C_{sp^3}, respectively. The final value of nonauthenticity factors: $R_1 = 0.0436$ (calculated on F for 1889 reflections with $I > 2\sigma(I)$), $wR_2 = 0.0947$ (calculated on F^2_{hkl} for all the 2530 reflections), GOF = 1.003, 289 refining parameters. All the calculations were made with the use of the SHELXTL PLUS 5 program package.[2]

3-Thio-5-R-1,2,4-triazol-4-amines were obtained according to the procedure described earlier.[3]

3-Benzylthio-1,2,4-triazoles 1a—c (general procedure). 4-Amino-5-R-1,2,4-triazole-3-thiol (10 mmol) was added to a solution of NaOH (10 mmol) in MeOH (15 mL). After dissolution of the triazole, *p*-nitrobenzyl bromide or benzyl bromide (10 mmol) was added. After several minutes, a formation of thick white precipitate was observed, which was filtered off, washed with water, and recrystallized from EtOH.

3-(4-Nitrobenzyl)thio-5-(pyridin-3-yl)-4*H*-1,2,4-triazole-4-amine (1a). The yield was 86%, m.p. 215 °C. Found (%): C, 51.37; H, 3.79; N, 25.76. $C_{14}H_{12}N_6O_2S$. Calculated (%): C, 51.20; H, 3.66; N, 25.60. ^{1}H NMR ($CDCl_3$), δ: 4.53, 4.57 (both s, 2 H each, SCH_2, NH_2); 7.41 (m, 1 H, Py); 7.63, 8.16 (both d, 2 H each, Ar, J = 8.8 Hz); 8.35 (d, 1 H, Py, J = 8.1 Hz); 8.69 (d, 1 H, Py, J = 5.0 Hz); 9.29 (s, 1 H, Py).

3-(4-Nitrobenzyl)thio-5-phenyl-4*H*-1,2,4-triazole-4-amine (1b). The yield was 73%, m.p. 209 °C. Found (%): C, 55.12; H, 4.01; N, 21.29. $C_{15}H_{13}N_5O_2S$. Calculated (%): C, 55.00; H, 3.98; N, 21.40. ^{1}H NMR ($CDCl_3$), δ: 4.47, 4.52 (both s, 2 H each, SCH_2, NH_2); 7.46 (m, 3 H, Ph); 7.62, 8.16 (both d, 2 H each, Ar, J = 8.5 Hz); 7.93 (m, 2 H, Ph).

3-(4-Nitrobenzyl)thio-5-(pyridin-4-yl)-4*H*-1,2,4-triazole-4-amine (1c). The yield was 70%, m.p. 218—220 °C. Found (%): C, 51.15; H, 3.67; N, 25.67. $C_{14}H_{12}N_6O_2S$. Calculated (%): C, 51.20; H, 3.66; N, 25.60. ^{1}H NMR ($CDCl_3$), δ: 4.58 (s, 4 H, SCH_2, NH_2); 7.64, 8.16 (both d, 2 H each, Ar, J = 8.5 Hz); 8.03, 8.72 (both d, 2 H each, Py, J = 6.2 Hz).

3-Benzylthio-5-(pyridin-4-yl)-4*H*-1,2,4-triazol-4-amine (1d). The yield was 73%, m.p. 186—188 °C. Found (%): C, 58.75; H, 3.87; N, 25.18. $C_{14}H_{13}N_5S$. Calculated (%): C, 59.34; H, 4.62; N, 24.72. ^{1}H NMR (DMSO-d_6), δ: 4.46 (s, 2 H, SCH_2); 6.23 (s, 2 H, NH_2); 7.26—7.35 (m, 3 H, Ph); 7.47 (d, 2 H, Ph); 7.99, 8.72 (both d, 2 H each, Py, J = 6.1 Hz).

Triazolothiadiazines 2a—e (general procedure). Equimolar amounts (5 mmol) of compound **1** and aromatic aldehyde were refluxed for 1—1.5 h in EtOH (10 mL) with catalytic amount of NaOH. After cooling, the reaction mixture was diluted with water, a precipitate was filtered off and recrystallized from MeCN.

6-(4-Bromophenyl)-7-(4-nitrophenyl)-3-(pyridin-3-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (2a). The yield was 65%, m.p. 280—282 °C. Found (%): C, 51.83; H, 3.88; N, 16.31. $C_{22}H_{19}BrN_6O_2S$. Calculated (%): C, 51,67; H, 3.74; N, 16.43. ^{1}H NMR (DMSO-d_6), δ: 5.02 (dd, 1 H, H(6), J = 10.2 Hz, J = 10.3 Hz); 5.25 (d, 1 H, H(7), J = 10.2 Hz); 7.24, 7.45 (both d, 2 H each, Ar, J = 8.1 Hz); 7.5 (m, 1 H, Py); 7.55 (d, 1 H, NH, J = 10.3 Hz); 7.70, 8.11 (both d, 2 H each, Ar, J = 8.5 Hz); 8.29 (d, 1 H, Py, J = 7.9 Hz); 8.65 (d, 1 H, Py, J = 4.1 Hz); 9.1 (s, 1 H, Py). MS (EI, 70 eV), m/z (I_{rel} (%)): 329 (3), 319 (22), 294 (10), 196 (32), 178 (60), 165 (25), 149 (23), 104 (83), 89 (100), 76 (80).

6-(4-Bromophenyl)-7-(4-nitrophenyl)-3-phenyl-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (2b). The yield was 79%, m.p. 280 °C. Found (%): C, 53.26; H, 3.09; N, 14.00. $C_{22}H_{16}BrN_5O_2S$. Calculated (%): C, 53.45; H, 3.26; N, 14.17. ^{1}H NMR (DMSO-d_6), δ: 5.0 (dd, 1 H, H(6), J = 10.0 Hz, J = 10.4 Hz); 5.2 (d, 1 H, H(7), J = 10.0 Hz); 7.26 (d, 2 H, Ar, J = 8.4 Hz); 7.42—7.47 (m, 5 H, Ph, Ar); 7.51 (d, 1 H, NH, J = 10.4 Hz); 7.71, 8.11 (both d, 2 H each, Ar, J = 8.6 Hz); 7.91—7.97 (m, 2 H, Ph). MS (EI, 70 eV), m/z (I_{rel} (%)): 495 $[M]^+$ (4), 493 $[M]^+$ (4), 461 (2), 360 (5), 328 (13), 312 (27), 196 (48), 177 (99), 149 (65), 105 (100), 77 (98).

6,7-Di(4-nitrophenyl)-3-phenyl-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (2c). The yield was 38%, m.p. 260 °C. Found (%): C, 57.63; H, 3.72; N, 18.11. $C_{22}H_{16}N_6O_4S$. Calculated (%): C, 57.39; H, 3.50; N, 18.25. ^{1}H NMR (DMSO-d_6), δ: 5.18—5.35 (m, 2 H, H(6), H(7)); 7.46 (m, 3 H, Ph); 7.58 (d, 2 H, Ar, J = 8.8 Hz); 7.67 (d, 1 H, NH, J = 10.1 Hz); 7.74 (d, 2 H, Ar, J = 8.7 Hz); 7.95 (m, 2 H, Ph); 8.12 (m, 4 H, Ar). MS (EI, 70 eV), m/z (I_{rel} (%)): 293 (2), 285 (3), 249 (2), 190 (7), 177 (27), 165 (15), 149 (19), 118 (23), 103 (100), 76 (77).

6-(3-Nitrophenyl)-7-(4-nitrophenyl)-3-(pyridin-4-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (2d). The yield was 34%, m.p. 180—182 °C. Found (%): C, 55.56; H, 4.14; N, 20.37. $C_{22}H_{19}N_7O_4S$. Calculated (%): C, 55.34; H, 4.01; N, 20.53. ^{1}H NMR (DMSO-d_6), δ: 5.27 (dd, 1 H, H(6), J = 10.1 Hz, J = 10.0 Hz); 5.40 (d, 1 H, H(7), J = 9.6 Hz); 7.57 (dd, 1 H, Ar, J = 7.7 Hz, J = 8.1 Hz); 7.67—7.77 (m, 3 H, Ar); 7.80 (d, 1 H, NH,

J = 10.0 Hz); 7.97 (d, 2 H, Py, *J* = 6.2 Hz); 8.05—8.17 (m, 3 H, Ar); 8.26 (s, 1 H, Ar); 8.71 (d, 2 H, Py, *J* = 6.1 Hz). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 295 (3), 284 (3), 264 (2), 191 (4), 178 (20), 165 (13), 149 (27), 104 (68), 89 (83), 78 (82), 51 (100).

6-(4-Bromophenyl)-7-(4-nitrophenyl)-3-(pyridin-4-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (2e). The yield was 52%, m.p. 278 °C. Found (%): C, 51.81; H, 3.86; N, 16.24. $C_{22}H_{19}BrN_6O_2S$. Calculated (%): C, 51,67; H, 3.74; N, 16.43. ^{1}H NMR (DMSO-d_6), δ: 5.02 (dd, 1 H, H(6), *J* = 10.6 Hz, *J* = 10.0 Hz); 5.27 (d, 1 H, H(7), *J* = 9.7 Hz); 7.27, 7.49 (both d, 2 H each, Ar, *J* = 8.4 Hz); 7.63 (d, 1 H, NH, *J* = 10.4 Hz); 7.73, 8.13 (both d, 2 H each, Ar, *J* = 8.7 Hz); 7.98, 8.71 (both d, 2 H each, Py, *J* = 5.8 Hz). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 319 (3), 313 (5), 280 (2), 196 (6), 178 (28), 162 (10), 149 (16), 104 (57), 89 (100), 78 (79), 50 (82).

3-(Benzylthio)-*N*-[(4-bromophenyl)methylidene]-5-(4-pyridin-4-yl)-4*H*-1,2,4-triazole-4-amine (3) was recrystallized from EtOH. The yield was 64%, m.p. 170 °C. Found (%): C, 57.24; H, 4.41; N, 15.63. $C_{21}H_{16}BrN_5S$. Calculated (%): C, 56.01; H, 3.58; N, 15.55. ^{1}H NMR (DMSO-d_6), δ: 4.45 (s, 2 H, SCH_2); 7.25—7.32 (m, 5 H, Ph); 7.79—7.87 (m, 6 H, Ar); 8.71 (d, 2 H, Py, *J* = 6.3 Hz); 8.82 (s, 1 H, N=CH).

(Triazol-3-ylthio)ethanimines (ethenamines) 4a,b (general procedure). Triazolothiadiazine **2a** or **2b** (1 mmol) was dissolved in DMF (5 mL), a solution of EtONa (4 mmol) in EtOH was added dropwise. After 15 min, the reaction mixture was diluted with water and neutralized with diluted AcOH. An orange precipitate formed was filtered off. The product was isolated by column chromatography (Al_2O_3, eluent: $CHCl_3$—CH_3CN, 5 : 1).

1-(4-Bromophenyl)-2-(4-nitrophenyl)-2-[5-(pyridin-3-yl)-1*H*-1,2,4-triazol-3-ylthio]ethanimine (4a). The yield was 87%, m.p. 125—127 °C. Found (%): C, 51.21; H, 3.28; N, 16.69. $C_{21}H_{15}BrN_6O_2S$. Calculated (%): C, 50.92; H, 3.05; N, 16.97. ^{1}H NMR (DMSO-d_6), δ: 6.61 (s, 1 H, SCH); 6.9 (s, 1 H, NH, imine); 7.18—7.36 (m, 4 H, Ar); 7.45—7.73 (m, 3 H, Ar); 7.89 (d, 2 H, Ar, *J* = 8.5 Hz); 8.25 (d, 1 H, Py, *J* = 7.9 Hz); 8.61 (d, 1 H, Py, *J* = 4.1 Hz); 9.1 (s, 1 H, Py); 14.04 (s, 1 H, NH, triazole). ^{1}H NMR ($CDCl_3$), δ: 5.25 (s, 2 H, NH_2); 7.05—7.61 (m, 7 H, Ar); 7.91 (d, 2 H, Ar, *J* = 8.5 Hz); 8.28 (d, 1 H, Py, *J* = 7.9 Hz); 8.65 (d, 1 H, Py, *J* = 4.1 Hz); 9.25 (s, 1 H, Py); 11.34 (s, 1 H, NH, triazole). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 494 $[M]^+$ (7), 461 (12), 318 (43), 193 (35), 183 (100), 165 (48), 102 (86), 76 (75), 44 (92).

1-(4-Bromophenyl)-2-(4-nitrophenyl)-2-(5-phenyl-1*H*-1,2,4-triazol-3-ylthio)ethanimine (4b). The yield was 92%, m.p. 121 °C. Found (%): C, 53.72; H, 3.56; N, 14.02. $C_{22}H_{16}BrN_5O_2S$. Calculated (%): C, 53.45; H, 3.26; N, 14.17. ^{1}H NMR (DMSO-d_6), δ: 6.66 (s, 1 H, SCH); 6.94 (s, 1 H, NH, imine); 7.19—7.62 (m, 9 H, Ar); 7.81—7.95 (m, 4 H, Ar); 13.75 (s, 1 H, NH, triazole). ^{1}H NMR ($CDCl_3$), δ: 5.18 (s, 2 H, NH_2); 7.16, 7.28 (both d, 2 H each, Ar, *J* = 8.35 Hz); 7.35—7.47 (m, 5 H, Ar); 7.83—7.93 (m, 4 H, Ar); 11.34 (s, 1 H, NH, triazole). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 495 $[M]^+$ (1.3), 493 $[M]^+$ (1.7), 462 (4), 312 (12), 223 (12), 185 (22), 183 (23), 165 (21), 104 (100), 77 (61).

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