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Synthesis of 3-R-4-substituted-Δ^2-1,2,4-triazoline-5-thione

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In the reaction of hydroiodide of methyl ester of *S*-methylthiosemicarbazide with secondary amines hydroiodides of 2-amino-1-substitutedguanidine were obtained (**1**). These compounds were then converted to respective 3-R-4-substituted Δ^2-1,2,4-triazoline-5-thione and (**2**) in the reactions with isothiocyanates.

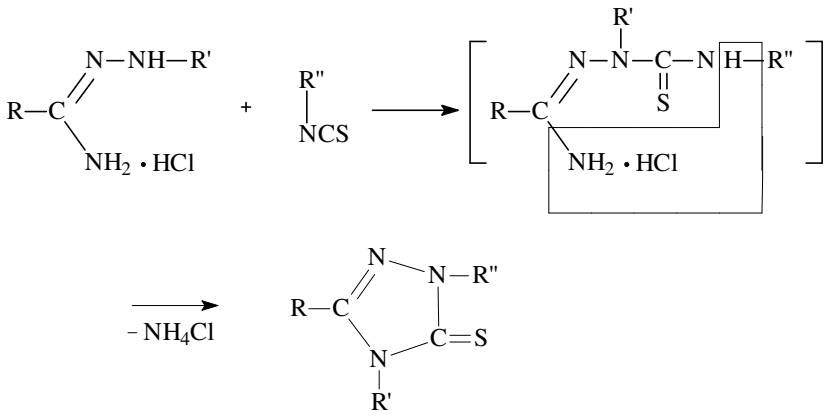
1. INTRODUCTION

The salts of aminoguanidine are used as starting materials for preparation of 3-amino-1,2,4-triazole and its derivatives which have numerous practical applications as the compounds of antiseptic action [1-18] The 3-amino-1,2,4-triazole known under the name of Amitrole or Amisole has also the herbicidal properties [19-22] Their presence in soils causes the increase of carbohydrates content in plants [23], inhibits the growth of *Ochromonas denica, Euglena gracilis and Spirodella digoriza* bacteria [23-28], as well as slows down their reproduction processes owing to photosynthesis inhibition.

The reactions of aminoguanidine salts with isothiocyanates lead to formation of hydrochlorides of 4-substituted derivatives of 1-amidinethiosemicarbazide [29] or *p*-toluenesulfonates [30]

Thiosemicarbazide derivatives cyclized in basic medium have converted to 4-substituted derivatives of 3-amino-1,2,4-triazoline-5-thione [23,30] whereas in acidic media the derivatives of 1,3,4-thiadiazole were formed [30]

Aminoguanidine salts have a composition similar to amidrazones salts, so they can give the similar reactions as amidrazones salts. The reaction of amidrazones salts with isothiocyanates leads to 3,4-disubstituted Δ^2-1,2,4-triazoline-5-thione according to Scheme 1 [31-33]



R, R', R" = alkyl, aryl

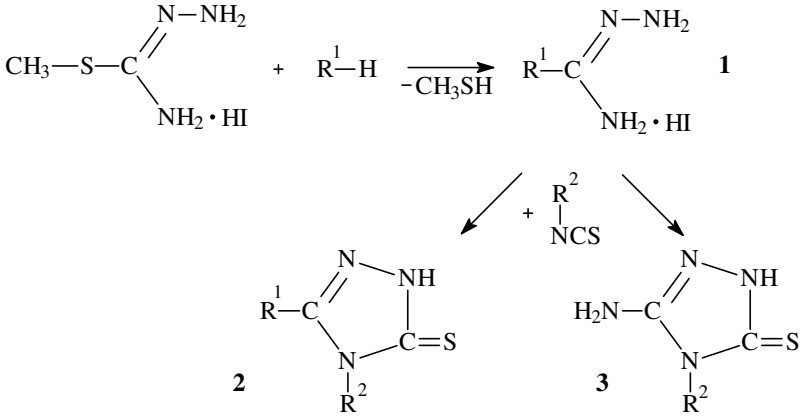
Scheme 1

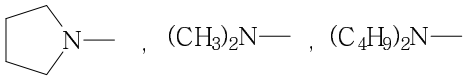
The similar course of the reaction cyclization with aromatic isothiocyanates is should in the case of use of the salts of aminoguanidine derivatives. The reactions of cyclization of derivatives of aminoguanidine salts, obtained in the reaction of hydroiodide of methyl ester of S-methylthiosemicarbazide with primary amines was described in previous papers [34-37] As a continuation of the previous studies this work presents the cyclization of reactions using secondary amines to obtain new derivatives of aminoguanidine salts.

2. RESULTS AND DISCUSSION

In this paper we report a formation of aminoguanidine salts in the reaction of hydroiodide of methyl ester of *S*-methylthiosemicarbazide with pyrrolidine, N,N-dimethylamine and N,N-dibutylamine. The products of above were cyclized by reaction with aromatic isothiocynates.

The reaction were performed according to the Scheme 2. The reactions of hydroiodide of *S*-methylthiosemicarbazide with pyrrolidine, N,N-dimethylamine and N,N-dibutylamine in dry methanol at room temperature were realized. The cyclization of new obtaining hydroiodides **(1)** with aromatic isothiocyanates was carried out in dry ethanol in boiling point for 3 h or in N,N- dimethylacetamide at temperature 60°C or 90°C for 5 h. The conditions of the reactions were established experimentally.



R^1 = 

R^2 = C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-BrC_6H_4

Based on the preliminary tests [38] it was found that depending on temperature the reaction had a two-pathway character (product (**2**) or product (**3**)). Product (**2**) was the result of the reaction carried out at 60-90°C. Product (**3**) was obtained by using aromatic isothiocyanates in the reaction at temperature 110-120°C. There were the same compounds as the ones obtained in the reaction of salts of aminoguanidine with aromatic isothiocyanates [38] Mixed melting points have not shown any depression. The IR and ^{1}H NMR spectra of compounds (**3**) were also identical with compounds described previously [38]

The structure of the new products obtained was confirmed by elemental analyses as well as by IR and ^{1}H NMR spectra.

3. EXPERIMENTAL

Melting points were determined in Fisher-Johns blocs and presented without any corrections. IR spectra were recorded in KBr using Specord IR-75 spectrophotometer. The ^{1}H NMR spectra were recorded on a Brucker Avance 300 in DMSO-d_6 with TMS as internal standard. The ^{13}C NMR spectra were recorded on a Brucker AC 200F in DMSO-d_6. Chemicals were purchased from Merck Co. or Fluka Ltd. and used without further purification. Purity was

checked by TLC on Merck Co. plates Aluminium oxide 60 F_{254} in a $CHCl_3/C_2H_5OH$ (10:1) solvent system with UV visualization.

Pyrrolidinamidrazon hydroiodide (1a), 2-amino-1-(N,N-dimethyl)-guanidine hydroiodide (1b) and 2-amino-1-(N,N-dibutyl)guanidine hydroiodide (1c)

2.3 g (0.01 mol) of hydroiodide of methyl ester of *S*-ethylthiosemicarbazide and 0.01 mol of amine dissolved in 30 ml of dry methanol were placed in reaction flask and kept for 48 h at room temperature. Then the reaction mixture was distilled under reduced pressure (water-solution pump) in order to removal methanol, and then the residue (1/3 of starting volume) was treated with dry ether. The product was filtered off, dried and finally crystallized from ethanol.

Pyrrolidinamidrazon hydroiodide (1a)

Yield 2.12g (83%); m.p. 154-155 ^oC. ^1H NMR (DMSO-d_6) δ/ppm: 1.86-1.96(m,4H,2CH_2), 3.23-3.37(m,4H,2CH_2), 4.76(s,2H,NH_2), 7.42(s,3H,NH_2^+H).

Anal. Calcd. for $C_5H_{13}N_4I$ (M = 256.1): C 23.45, H 5.16, N 21.88%; found C 22.94, H 5.51, N 20.67%.

2-Amino-1-(N,N-dimethyl)guanidine hydroiodide (1b)

Yield 1.93g (84%); m.p. 119-121 ^oC. ^1H NMR (DMSO-d_6) δ/ppm: 2.55(s,6H,CH_3), 7.08(s,3H,NH_2^+H), 8.55(s,2H,NH_2).

Anal. Calcd. for $C_3H_{11}N_4I$ (M = 230.1): C 15.66, H 4.82, N 24.35%; found C 14.94, H 4.05, N 23.87%.

2-Amino-1-(N,N-dibutyl)guanidine hydroiodide (1c)

Yield 2.67g (85%); mp 202-204 ^oC. ^1H NMR (DMSO-d_6) δ/ppm: 0.80-0.96(m,4H,2CH_2), 1.41-1.78(m,8H,4CH_2), 2.97(m,6H,2CH_3) 5.58(s,2H,NH_2), 7.12(s,3H,NH_2^+H).

Anal. Calcd. for $C_9H_{23}N_4I$ (M = 314.2): C 34.40, H 7.38, N 17.83%; found C 33.92, H 7.40, N 17.91%.

3-Pyrrolidine-4-substituted-Δ^2-1,2,4-triazoline-5-thione (2a-2d), 3-(N,N-dimethyl)amino-4-substituted Δ^2-1,2,4-triazoline-5-thione (2e-2h) and 3-(N,N-dibutyl)amino-4-substituted Δ^2-1,2,4-triazoline-5-thione and (2i-2l)

a) Procedure for ***2b, 2j, 2l***.

0.01 mol of hydroiodides (**1a** or **1c**) and 0.01 mol of aromatic isothiocyanates dissolved in 30 ml of dry ethanol were refluxed for 3 h. Then the reaction mixture was distilled under reduced pressure. The product of the reaction was washed carefully with water and ether, dried and crystallized from ethanol .

3-Pyrrolidine-4-(4-methylphenyl)-Δ^2-1,2,4-triazoline-5-thione (2b)

Yield 1.69g (65%); m.p. 183-185 ^{o}C. IR (KBr) ν_{max}/cm^{-1}: 3379 NH, 2972 CH arom., 1457 CH aliph., 1626 C=N, 1506 C-N, 1359 C=S. ^{1}H NMR (DMSO-d_6) δ/ppm: 1.93-2.18 (m,4H,2CH_2), 2.19(s,3H,CH_3), 3.36-3.40(m,4H,2CH_2), 6.91-7.55 (m,4H,arom.), 7.93, 9.99(2s,1H,NH-C=S).

Anal. Calcd. for $C_{13}H_{16}N_4S$ (M = 260.4): C 59.97, H 6.19, N 21.52%; found C 59.86, H 6.91, N 22.00%.

3-(N,N-dibutyl)amino-4-(4-methylphenyl)-Δ^2-1,2,4-triazoline-5-thione(2j)

Yield 2.01g (63%); m.p. 78-80 ^{o}C. IR (KBr) ν_{max}/cm^{-1}: 3223 NH, 3043 CH arom., 2989, 1462 CH aliph., 1595 C=N, 1538 C-N, 1373 C=S. ^{1}H NMR (DMSO-d_6) δ/ppm: 0.83-0.96(m,4H,2CH_2), 1.24-1.62(m,8H,4CH_2), 2.26(s,3H,CH_3), 4.39-4.52(m,6H,2CH_3), 7.08-7.47(m,4H,arom.), 10.98(s,1H,NH-C=S).

Anal. Calcd. for $C_{17}H_{26}N_4S$ (M = 318.5): C 64.11, H 8.23, N 17.59%; found C 64.04, H 8.05, N 17.34%.

3-(N,N-dibutyl)amino-4-(4-bromophenyl)-Δ^2-1,2,4-triazoline-5-thione (2l)

Yield 3.33g (87%); m.p. 101-103 ^{o}C. IR (KBr) ν_{max}/cm^{-1}: 3236 NH, 3049 CH arom., 2986, 1465 CH aliph., 1595 C=N, 1545 C-N, 1376 C=S. ^{1}H NMR (DMSO-d_6) δ/ppm: 0.82-0.96(m,4H,2CH_2), 1.07-1.62(m,8H,4CH_2), 2.48-2.96(m,6H,2CH_3), 7.50-7.56 (m,4H,arom.), 11.18(s,1H,NH-C=S). ^{13}C NMR (DMSO-d_6) δ/ppm: 13.4(2*C*H_3), 19.2(2CH_3*C*$H_2$$CH_2$$CH_2$), 27.5(2$CH_3$$CH_2$*C*$H_2$$CH_2$), 56.0 (2$CH_3$$CH_2$$CH_2$*C*$H_2$), 116.6(*C*Br), 124.1, 131.4(*C*=*C*,*C*=*C*$_{aromat}$), 137.6(*C*-N), 153.8(*C*=N), 187.4(*C*=S).

Anal. Calcd. for $C_{16}H_{23}N_4SBr$ (M = 383.3): C 50.13, H 6.05, N 14.62%; found C 50.90, H 5.94, N 14.61%.

b) Procedure for ***2a, 2f, 2g, 2i, 2k***

0.01 mol of hydroiodide (**1a-1c**) and 0.01 mol of aromatic isothiocyanates dissolved in 20 ml of *N,N*-dimethylacetamide were placed in a round-bottomed flask and heated for 5 h on an oil bath at temperature 90°C for compounds **2a**, **2f**, **2k** and at temperature 60°C for compounds **2g** and **2i**. Then the reaction mixture was distilled under reduced pressure. The product of the reaction was washed carefully with water and ethyl ether, dried and crystallized from dry ethanol .

3-Pyrrolidine-4-phenyl-Δ^2-1,2,4-triazoline-5-thione (2a)

Yield 1.48g (60%); m.p. 179-180 °C. IR (KBr) ν_{max}/cm^{-1}: 3420 NH, 2961 CH arom., 1629 C=N, 1500 C-N, 1360 C=S. ^{1}H NMR (DMSO-d_6) δ/ppm: 1.89-2.02(m,4H,2CH_2), 3.34-3.39(m,4H,2CH_2), 6.65-7.66(m,5H,arom.), 8.03,10.00(2s, 1H, NH-C=S).

Anal. Calcd. for $C_{12}H_{14}N_4S$ (M = 246.3): C 58.51, H 5.73, N 22,75%; found C 58.26, H 5.67, N 22.74%.

3-(N,N-dimethyl)amino-4-(4-methylphenyl)-Δ^2-1,2,4-triazoline-5-thione (2f)

Yield 1.76g (75%); m.p. 223-224 °C. IR (KBr) ν_{max}/cm^{-1}: 3441 NH, 3083 CH arom., 2925,1482 CH aliph., 1588 C=N, 1512 C-N, 1368 C=S. ^{1}H NMR (DMSO-d_6) δ/ppm: 2.27(s,6H,2CH_3), 2.39(s,3H,CH_3), 7.08-7.42(m,4H,arom.), 9.58,13.95(2s, 1H, NH-C=S).

Anal. Calcd. for $C_{11}H_{14}N_4S$ (M = 234.3): C 56.38, H 6.02, N 23.91%; found C 57.02, H 5.84, N 23.63%.

3-(N,N-dimethyl)amino-4-(4-methoxyphenyl)-Δ^2-1,2,4-triazoline-5-thione (2g)

Yield 1.75g (70%); m.p. 135-137 °C. IR (KBr) ν_{max}/cm^{-1}: 3246 NH, 3047 CH arom., 2932,1462 CH aliph., 1605 C=N, 1512 C-N, 1369 C=S, 1250 C-O-C. ^{1}H NMR (DMSO-d_6) δ/ppm: 2.53(s,6H,2CH_3), 3.73(s, 3H, CH_3), 7.04-7.53(m, 4H, arom.), 10.14,13.95 (2s,1H,NH-C=S).

Anal. Calcd. for $C_{11}H_{14}N_4OS$ (M = 250.3): C 52.78, H 5.64, N 22.38%; found C 52.65, H 5.14, N 22.13%.

3-(N,N-dibutyl)amino-4-phenyl-Δ^2-1,2,4-triazoline-5-thione (2i)

Yield 2.13g (70%); m.p. 128-130 °C. IR (KBr) ν_{max}/cm^{-1}: 3206 NH, 3034 CH arom., 3009,1450 CH aliph., 1599 C=N, 1553 C-N, 1382 C=S. ^{1}H NMR (DMSO-d_6) δ/ppm: 0.82-0.94(m,4H,2CH_2), 1.41-1.80(m,8H,2CH_2), 2.79-2.95(m,6H,2CH_3), 7.10-7.56(m,5H,arom.), 9.83(s,1H,NH-C=S).

Anal. Calcd. for $C_{16}H_{24}N_4S$ (M = 304.4): C 63.12, H 7.95, N 18.41%; found C 64.12, H 7.94, N 18.41%.

3-(N,N-dibutyl)amino-4-(4-methoxyphenyl)-Δ^2-1,2,4-triazoline-5-thione (2k)

Yield 2.79g (83%); m.p. 166-168 °C. IR (KBr) ν_{max}/cm^{-1}: 3410 NH, 2928 CH arom., 1587 C=N, 1512 C-N, 1460 CH aliph., 1370 C=S, 1244 C-O-C. ^{1}H NMR (DMSO-d_6) δ/ppm: 0.81-0.96(m,4H,2CH_2), 1.15-1.56(m,8H,4CH_2), 2.47-2.94(m,6H,2CH_3), 3.74(s,3H,CH_3), 6.84-7.36(m,4H,arom.), 9.42(s,1H,NH-C=S).

Anal. Calcd. for $C_{17}H_{26}N_4OS$ (M = 334.5): C 61.04, H 7.84, N 16.75%; found C 61.03, H 7.05, N 16.73%.

c) Procedure for ***2c, 2d, 2e, 2h.***

0,01 Mol of hydroiodides **1a** or **1b** and 0.01 mole of isothiocyanates dissolved in 30 ml of dry ethanol and was kept for 24 h at room temperature. Then the reaction mixture was distilled under the reduced pressure. The product of the reaction was washed with ether, dried and crystallized from ethanol.

3-Pyrrolidine-4-(4-methoxyphenyl)-Δ^2-1,2,4-triazoline-5-thione (2c)

Yield 1.93g (70%); m.p. 168-170 °C. IR (KBr) ν_{max}/cm^{-1}: 3382 NH, 2956 CH arom., 1657 C=N, 1522 C-N, 1468 CH aliph., 1353 C=S, 1250 C-O-C. ^{1}H NMR (DMSO-d_6) δ/ppm: 1.84-1.93(m,4H,2CH_2), 3.34-3.47(m,4H,2CH_2), 3.76(s,3H,CH_3), 6.90-7.36(m,4H,arom.), 7.78,9.95(2s, 1H, NH-C=S).

Anal. Calcd. for $C_{13}H_{16}N_4OS$ (M = 276.4): C 56.49, H 5.84, N 20.27%; found: C 56.07, H 5.67, N 21.04%.

3-Pyrrolidine-4-(4-bromophenyl)-Δ^2-1,2,4-triazoline-5-thione (2d)

Yield 2.99g (92%); m.p. 174-175 °C. IR (KBr) ν_{max}/cm^{-1}: 3378 NH, 2957 CH arom., 1621 C=N, 1535 C-N, 1386 C=S. ^{1}H NMR (DMSO-d_6) δ: 1.86-

2.02(m,4H,2CH_2), 3.23-3.68(m,4H,2CH_2), 7.22-7.68(m,4H,arom.), 8.29,9.96 (2s, 1H, NH-C=S). ^{13}C NMR (DMSO-d_6) δ/ppm: 24.6(2*C*H_2), 40.3(2*C*H_2N), 116.3(*C*Br), 127.5, 130.6(*C*=*C*,*C*=C_{aromat}), 130.7(*C*-N), 140.0(*C*=N), 177.2(*C*=S).

Anal. Calcd. for $C_{12}H_{13}N_4SBr$ (M = 325.2): C 44.31, H 4.03, N 12.23%; found: C 43.86, H 4.02, N 12.52%.

3-(N,N-dimethyl)amino-4-phenyl-Δ^2-1,2,4-triazoline-5-thione (2e)

Yield 1.67g (76%); m.p. 185-187 °C. IR (KBr) ν_{max}/cm^{-1}: 3298 NH, 3087 CH arom., 2956,1453 CH aliph., 1594 C=N, 1568 C-N, 1367 C=S. ^{1}H NMR (DMSO-d_6) δ/ppm: 2.51(s,6H,2CH_3), 7.54-7.65(m,5H,arom.), 10.37,14.04(2s, 1H, NH-C=S). ^{13}C NMR (DMSO-d_6) δ/ppm: 13.7(2*C*H_3), 128.0, 129.1, 129.4(C_{aromat}), 150.1(*C*-N), 164.3(*C*=N), 168.3(*C*=S).

Anal. Calcd. for $C_{10}H_{12}N_4S$ (M = 220.3): C 54.52, H 5.49, N 25.44%; found C 55.12, H 5.14, N 25.23%.

3-(N,N-dimethyl)amino-4-(4-bromophenyl)-Δ^2-1,2,4-triazoline-5-thione (2h)

Yield 2.18g (73%); m.p. 191-193 °C. IR (KBr) ν_{max}/cm^{-1}: 3341 NH, 3090 CH arom., 2965,1468 CH aliph, 1597 C=N, 1511 C-N, 1358 C=S. ^{1}H NMR (DMSO-d_6) δ/ppm: 2.51(s,6H,2CH_3), 7.36-7.82(m,4H,arom.), 10.49,14.05(2s, 1H, NH-C=S).

Anal. Calcd. for $C_{10}H_{11}N_4SBr$ (M = 299.2): C 40.14, H 3.71, N 18.73%; found C 39.84, H 3.65, N 18.62%.

3-Amino-4-substituted Δ^2-1,2,4-triazoline-5-thione (3)

General procedure:

0.01 mol of hydroiodide (**1a-1c**) and 0.01 mol of aromatic isothiocyanates dissolved in 20 ml of *N,N*-dimethylacetamide were placed in a round-bottomed flask and heated for 5 h on an oil bath at temperature 110-120°C. Then the reaction mixture was distilled under reduced pressure. The product of the reaction was washed carefully with water and ether, dried and crystallized fromdry ethanol.

3-Amino-4-phenyl-Δ^2-1,2,4-triazoline-5-thion ***(3a)***: m.p. 268-269 °C, lit. [38] , m.p. 267-268 °C. Yield 84%.

3-Amino-4-(4-methylphenyl)-Δ^2-1,2,4-triazoline-5-thion ***(3b)***: m.p. 286-287 °C, lit. [38], m.p. 286-287 °C. Yield 90%.

3-Amino-4-(4-methoxyphenyl)-Δ^2 -1,2,4-triazoline-5-thion **(3c)**: m.p. 255-257 °C, lit. [38], m.p. 255-256 °C. Yield 86%.
*3-Amino-4-(4-bromophenyl)-Δ^2 -1,2,4-triazoline-5-thion **(3d)***: m.p. 290-292 °C, lit. [38], m.p. 289-290 °C. Yield 82%.

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