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THE REACTIONS OF HYDROIODIDE OF 2-AMINO-1-SUBSTITUTED GUANIDINE DERIVATIVES WITH AROMATIC ISOTHIOCYANATES

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

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.

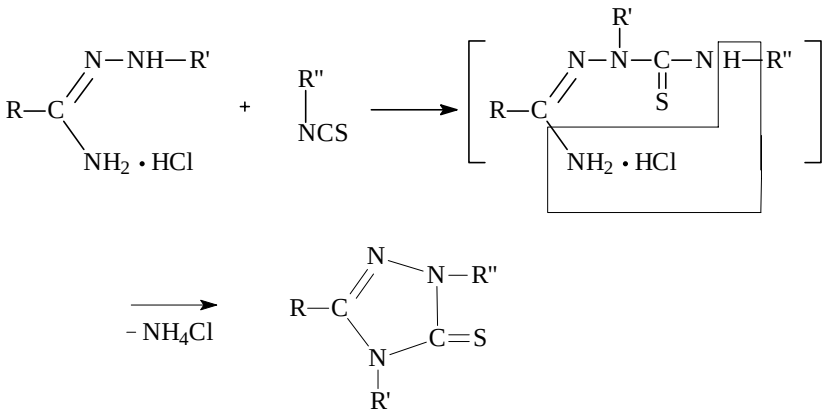
The reactions of aminoguanidine salts with isothiocyanates lead to formation of hydrochlorides of 4-substituted derivatives of 1-amidinethiosemicarbazide[29] or *p*-toluenesulfonates.[30]

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.[31,32]

The similar course of the reaction cyclization with aromatic isothiocyanates is should in the case of use of the salts of aminoguanidine derivatives.

Scheme 1



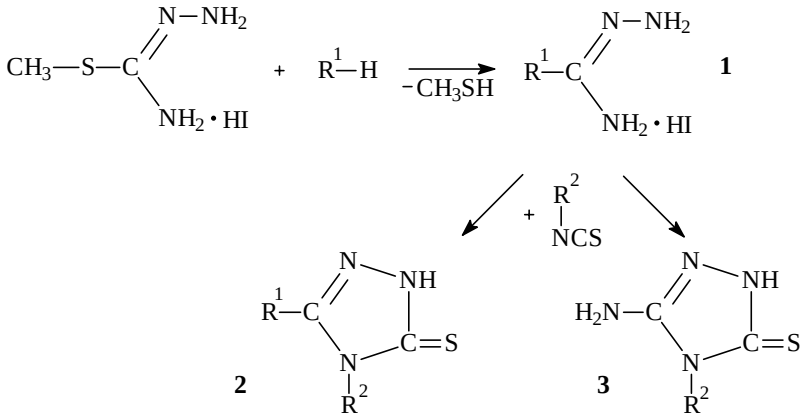
R, R', R" = alkyl, aryl

RESULTS AND DISCUSSION

In this paper we report a formation of aminoguanidine salts in the reaction of hydroiodide of *S*-methylthiosemicarbazide with aniline, 3-toluidine and benzylamine. The products of above were cyclized by reaction with aromatic isothiocynates.

The reaction were performed according to the Scheme 2.

Scheme 2



The reactions of hydroiodide of *S*-methylthiosemicarbazide with aniline, 3-toluidine and benzylamine 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 90°C for 5 h. The conditions of the reactions were established experimentally.

Based on the preliminary tests[33] 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 78-

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.[33] 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.[33]

Table 1

Product		Yield [%]
	R^1	
1a	C_6H_5NH-	84
1b	3-$CH_3C_6H_4NH$-	90
1c	$C_6H_5CH_2NH$-	79

Table 2

Product			Yield [%]
	R^1	R^2	
2a	C_6H_5NH-	C_6H_5	72
2b	C_6H_5NH-	4-$CH_3C_6H_4$	70
2c	C_6H_5NH-	4-$CH_3OC_6H_4$	65
2d	3-$CH_3C_6H_4NH$-	C_6H_5	72
2e	3-$CH_3C_6H_4NH$-	4-$CH_3C_6H_4$	75
2f	3-$CH_3C_6H_4NH$-	4-$CH_3OC_6H_4$	78
2g	$C_6H_5CH_2NH$-	C_6H_5	70
2h	$C_6H_5CH_2NH$-	4-$CH_3C_6H_4$	64
2i	$C_6H_5CH_2NH$-	4-$CH_3OC_6H_4$	52

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

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 Tesla BS-567 A spectrometer (100 MHz) in DMSO-d_6 with TMS as internal standard. 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.

2-Amino-1-phenylguanidine hydroiodide **(1a)**, 2-amino-1-(3-tolyl)guanidine hydroiodide **(1b)** and 2-amino-1-benzylguanidine hydroiodide **(1c)**

2.3 g (0.01 mol) of hydroiodide of *S*-methylthiosemicarbazide and 0.01 mol of amine dissolved in 30 mL of dry methanol were placed in reaction flask and kept for 48 h at rt. 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 (79-90%). The results are collected in the Table 1.

2-Amino-1-phenylguanidine hydroiodide **(1a)**: mp 124-125 ^oC. ^1H NMR (DMSO-d_6) δ: 5.72(s, 2H, N**H**$_2$); 7.20-7.60(m, 5H, arom); 7.83(s, 3H, N**H**$_2^+$**H**); 10.35(s, 1H, N**H**). *Anal.* Calcd for $C_7H_{11}N_4I$: C 30.23, H 3.99, N 20.15. Found: C 30.15, H 4.31, N 21.01.

2-Amino-1-(3-tolyl)guanidine hydroiodide **(1b)**: mp 116-118 ^oC. ^1H NMR (DMSO-d_6) δ: 2.50(s, 3H, C**H**$_3$); 5.98(s, 2H, N**H**$_2$); 7.30-7.64(m, 4H, arom); 7.92(s, 3H, N**H**$_2^+$**H**); 10.35(s, 1H, N**H**). *Anal.* Calcd for $C_8H_{13}N_4I$: C 32.89, H 4.49, N 19.18. Found: C 33.70, H 4.80, N 19.91.

2-Amino-1-benzylguanidine hydroiodide **(1c)**: mp 123-125 ^oC. ^1H NMR (DMSO-d_6) δ: 4.43(d, 2H, C**H**$_2$); 5.61(s, 2H, N**H**$_2$); 7.11-7.46(m, 5H, arom); 7.91(s, 3H, N**H**$_2^+$**H**); 8.66(s, 1H, N**H**). *Anal.* Calcd for $C_8H_{13}N_4I$: C 32.89, H 4.49, N 19.18. Found: C 33.12, H 4.52, N 19.31.

3-Arylamino-4-substituted Δ^2-1,2,4-triazoline-5-thione **(2a-2f)** and 3-benzylamino-4-substituted Δ^2-1,2,4-triazoline-5-thione and **(2g-2i)**

a) Procedure for **2c, 2e,2f, 2g, 2h, 2i**.

0.01 Mol of hydroiodides (**1a-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 (52-78%). The results are collected in the Table 2.

3-Phenylamino-4-(4-methoxyphenyl)-Δ^2-1,2,4-triazoline-5-thione **(2c)**: mp 205-207 ^oC. IR (cm^{-1}): 3340 NH; 3007 CH arom; 2967, 1456 CH aliph; 1588 C=N; 1513 C-N; 1316 C=S; 1250 C-O-C. ^1H NMR (DMSO-d_6) δ: 3.83(s, 3H, C**H**$_3$); 7.14-7.37(m, 9H, arom); 10.93(s, 1H, N**H**); 13.97(2s, 1H, N**H**-C=S). *Anal.* Calcd for $C_{15}H_{14}N_4OS$: C 60.38, H 4.73, N 18.78. Found: C 61.11, H 4.55, N 18.54.

3-(3-Tolyl)amino-4-(4-methylphenyl)-Δ^2-1,2,4-triazoline-5-thione **(2e)**: mp 133-136 ^oC. IR (cm^{-1}): 3248 NH; 3042 CH arom; 2923, 1458 CH aliph; 1572 C=N; 1515 C-N; 1373 C=S. ^1H NMR (DMSO-d_6) δ: 2.08(s, 3H, C**H**$_3$); 2.39(s, 3H, C**H**$_3$); 7.09-7.50(m, 8H, arom); 10.23(s, 1H, N**H**); 13.97(s, 1H, N**H**-C=S). *Anal.* Calcd for $C_{16}H_{16}N_4S$: C 64.84, H 5.44, N 18.90. Found: C 64.54, H 5.51, N 18.84.

3-(3-Tolyl)amino-4-(4-methoxyphenyl)-Δ^2-1,2,4-triazoline-5-thione **(2f)**: mp 142-144 ^{o}C. IR (cm^{-1}): 3232 NH; 3038 CH arom; 2970, 1462 CH aliph; 1595 C=N; 1511 C-N; 1378 C=S; 1257 C-O-C. ^{1}H NMR (DMSO-d_6) δ: 2.65(s, 3H, C**H**$_3$); 3.73(s, 3H, C**H**$_3$); 7.04-7.53(m, 8H, arom); 10.14(s, 1H,N**H**); 13.94(s, 1H, N**H**-C=S). *Anal.* Calcd for $C_{16}H_{16}N_4OS$: C 61.58, H 5.16, N 17.94. Found: C 61.50, H 5.12, N 17.84.

3-Benzylamino-4-phenyl-Δ^2-1,2,4-triazoline-5-thione **(2g)**: mp 180-182 ^{o}C. IR (cm^{-1}): 3169 NH; 3047 CH arom; 2959, 1459 CH aliph; 1596 C=N; 1548 C-N; 1364 C=S. ^{1}H NMR (DMSO-d_6) δ: 4.48(d, *J*=5.6 Hz, 2H, C**H**$_2$); 7.19-7.57(m, 10H, arom); 9.96(s, 1H, N**H**); 10.25(s, 1H, N**H**-C=S). *Anal.* Calcd for $C_{15}H_{14}N_4S$: C 63.80, H 4.50, N 19.84. Found: C 63.54, H 4.44, N 19.73.

3-Benzylamino-4-(4-tolyl)-Δ^2-1,2,4-triazoline-5-thione **(2h)**: mp 163-165 ^{o}C. IR (cm^{-1}): 3149 NH; 3045 CH arom; 2949, 1457 CH aliph; 1589 C=N; 1510 C-N; 1347 C=S. ^{1}H NMR (DMSO-d_6) δ: 2.27(s, 3H, C**H**$_3$); 4.72(d, *J*=5.6 Hz, 2H, C**H**$_2$); 7.08-7.85(m, 9H, arom); 9.59(s, 1H, N**H**); 10.17(s, 1H, N**H**-C=S). *Anal.* Calcd for $C_{16}H_{16}N_4S$: C 64.84, H 5.44, N 18.90. Found: C 64.53, H 5.28, N 18.98.

3-Benzylamino-4-(4-methoxyphenyl)-Δ^2-1,2,4-triazoline-5-thione **(2i)**: mp 65-66 ^{o}C. IR (cm^{-1}): 3152 NH; 3063 CH arom; 2950, 1446 CH aliph; 1591 C=N; 1514 C-N; 1360 C=S; 1262 C-O-C. ^{1}H NMR (DMSO-d_6) δ: 3.74(s, 3H, C**H**$_3$); 4.49(d, *J*=5.7 Hz, 2H, C**H**$_2$); 6.85-7.52(m, 9H, arom); 9.42(s, 1H, N**H**); 10.91(s, 1H, N**H**-C=S). *Anal.* Calcd for $C_{16}H_{16}N_4OS$: C 61.50, H 5.16, N 17.94. Found: C 61.28, H 5.07, N 17.80.

b) Procedure for **2a**, **2b**, **2d**

0.01 Mol of hydroiodide (**1a-1b**) 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^{o}C. 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 (70-72%). The results are collected in the Table 2.

3-Phenylamino-4-phenyl-Δ^2-1,2,4-triazoline-5-thione **(2a)**: mp 165-167 ^{o}C. IR (cm^{-1}): 3427 NH; 2959 CH arom; 1597 C=N; 1548 C-N; 1368 C=S. ^{1}H NMR (DMSO-d_6) δ: 7.06-7.61(m, 10H, arom); 10.35(s, 1H, N**H**); 14.02(s, 1H, N**H**-C=S). *Anal.* Calcd for $C_{14}H_{12}N_4S$: C 62.66, H 4.51, N 20.88. Found: C 62.24, H 4.34, N 20.63.

3-Phenylamino-4-(4-methylphenyl)-Δ^2-1,2,4-triazoline-5-thione **(2b)**: mp 80-82 ^{o}C. IR (cm^{-1}): 3501 NH; 3097 CH arom; 2968, 1457 CH aliph; 1572 C=N; 1514 C-N; 1365 C=S. ^{1}H NMR (DMSO-d_6) δ: 2.50(s, 3H, C**H**$_3$); 7.09-7.51(m, 9H, arom); 10.24(s, 1H, N**H**); 13.97(s, 1H, N**H**-C=S). *Anal*. Calcd for $C_{15}H_{14}N_4S$: C 63.80, H 5.00, N 19.84. Found: C 63.64, H 5.01, N 19.64.

3-(3-Tolyl)amino-4-phenyl-Δ^2-1,2,4-triazoline-5-thione **(2d)**: mp 135-137 ^{o}C. IR (cm^{-1}): 3504 NH; 3095 CH arom; 2958, 1452 CH aliph; 1594 C=N; 1546 C-N; 1367 C=S. ^{1}H NMR (DMSO-d_6) δ: 2.51(s, 3H, C**H**$_3$); 7.35-7.64(m, 9H, arom); 10.35(s, 1H, N**H**); 14.00(s, 1H, N**H**-C=S). *Anal.* Calcd for $C_{15}H_{14}N_4S$:

C 63.80, H 4.50, N 19.84. Found: C 63.54, H 4.52, N 19.83.

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 (82-90%).

3-Amino-4-phenyl-Δ^2-1,2,4-triazoline-5-thion **(3a)**: mp 268-269 °C, lit., [34] mp 267-268 °C. Yield 84%.

3-Amino-4-(4-methylphenyl)-Δ^2-1,2,4-triazoline-5-thion **(3b)**: mp 286-287 °C, lit., [34] mp 286-287 °C. Yield 90%.

3-Amino-4-(4-methoxyphenyl)-Δ^2-1,2,4-triazoline-5-thion **(3c)**: mp 255-257 °C, lit., [34] mp 255-256 °C. Yield 86%.

3-Amino-4-(4-bromophenyl)-Δ^2-1,2,4-triazoline-5-thion **(3d)**: mp 290-292 °C, lit., [34] mp 289-290 °C. Yield 82%.

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