

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*-methylthiosemicarbazide 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.

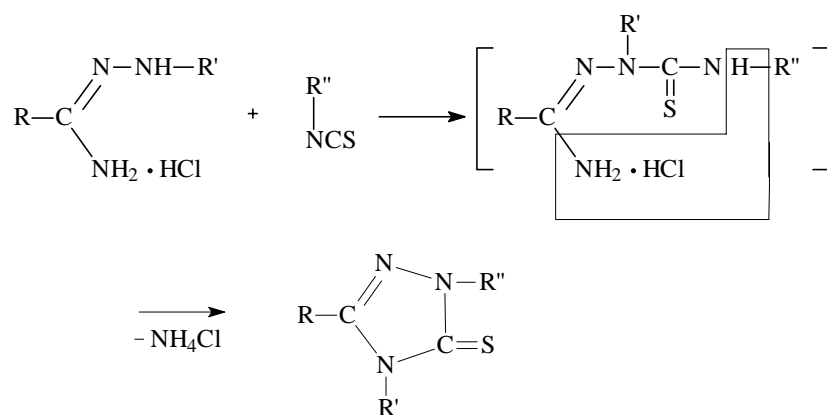
The reactions of aminoguanidine salts with isothiocyanates lead to formation of hydrochlorides of 4-substituted derivatives of 1-amidinethiosemicarbazide²⁹ or *p*-toluenesulfonates.³⁰

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



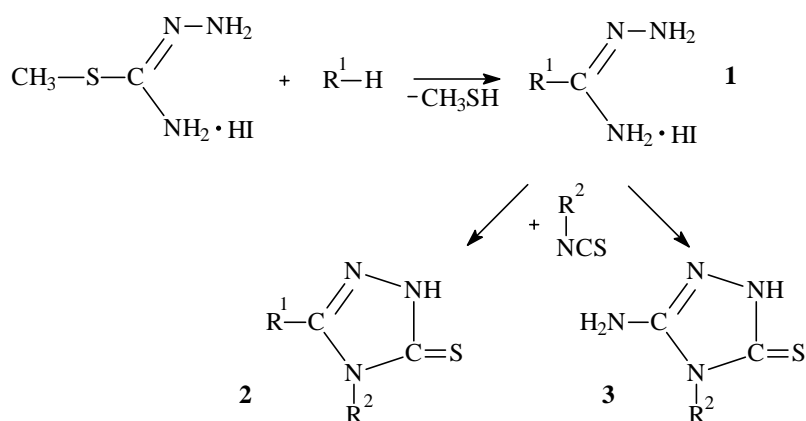
R, R', R'' = alkyl, aryl

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 isothiocyanates.

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 tests³³ 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 ¹H NMR spectra of compounds (**3**) were also identical with compounds described previously.³³

Table 1

Product		Yield
	R ¹	[%]
1a	C ₆ H ₅ NH-	84
1b	3-CH ₃ C ₆ H ₄ NH-	90
1c	C ₆ H ₅ CH ₂ NH-	79

Table 2

Product			Yield
	R ¹	R ²	[%]
2a	C ₆ H ₅ NH-	C ₆ H ₅	72
2b	C ₆ H ₅ NH-	4-CH ₃ C ₆ H ₄	70
2c	C ₆ H ₅ NH-	4-CH ₃ OC ₆ H ₄	65
2d	3-CH ₃ C ₆ H ₄ NH-	C ₆ H ₅	72
2e	3-CH ₃ C ₆ H ₄ NH-	4-CH ₃ C ₆ H ₄	75
2f	3-CH ₃ C ₆ H ₄ NH-	4-CH ₃ OC ₆ H ₄	78
2g	C ₆ H ₅ CH ₂ NH-	C ₆ H ₅	70
2h	C ₆ H ₅ CH ₂ NH-	4-CH ₃ C ₆ H ₄	64
2i	C ₆ H ₅ CH ₂ NH-	4-CH ₃ OC ₆ H ₄	52

The structure of the new products obtained was confirmed by elemental analyses as well as by IR and ¹H 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 ¹H NMR spectra were recorded on Tesla BS-567 A spectrometer (100 MHz) in DMSO-d₆ 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 F₂₅₄ in a CHCl₃/C₂H₅OH (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 °C. ¹H NMR (DMSO-d₆) δ: 5.72(s, 2H, NH₂); 7.20-7.60(m, 5H, arom); 7.83(s, 3H, NH₂⁺H); 10.35(s, 1H, NH). *Anal.* Calcd for C₇H₁₁N₄I: 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 °C. ¹H NMR (DMSO-d₆) δ: 2.50(s, 3H, CH₃); 5.98(s, 2H, NH₂); 7.30-7.64(m, 4H, arom); 7.92(s, 3H, NH₂⁺H); 10.35(s, 1H, NH). *Anal.* Calcd for C₈H₁₃N₄I: 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 °C. ¹H NMR (DMSO-d₆) δ: 4.43(d, 2H, CH₂); 5.61(s, 2H, NH₂); 7.11-7.46(m, 5H, arom); 7.91(s, 3H, NH₂⁺H); 8.66(s, 1H, NH). *Anal.* Calcd for C₈H₁₃N₄I: C 32.89, H 4.49, N 19.18. Found: C 33.12, H 4.52, N 19.31.

3-Arylamino-4-substituted Δ²-1,2,4-triazoline-5-thione (2a-2f) and 3-benzylamino-4-substituted Δ²-1,2,4-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)-Δ²-1,2,4-triazoline-5-thione (2c): mp 205-207 °C. 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-d₆) δ: 3.83(s, 3H, CH₃); 7.14-7.37(m, 9H, arom); 10.93(s, 1H, NH); 13.97(2s, 1H, NH-C=S). *Anal.* Calcd for C₁₅H₁₄N₄OS: 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)-Δ²-1,2,4-triazoline-5-thione (2e): mp 133-136 °C. IR (cm⁻¹): 3248 NH; 3042 CH arom; 2923, 1458 CH aliph; 1572 C=N; 1515 C-N; 1373 C=S. ¹H NMR (DMSO-d₆) δ: 2.08(s, 3H, CH₃); 2.39(s, 3H, CH₃); 7.09-7.50(m, 8H, arom); 10.23(s, 1H, NH); 13.97(s, 1H, NH-C=S). *Anal.* Calcd for C₁₆H₁₆N₄S: 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 °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. ¹H NMR (DMSO-d₆) δ : 2.65(s, 3H, CH₃); 3.73(s, 3H, CH₃); 7.04-7.53(m, 8H, arom); 10.14(s, 1H, NH); 13.94(s, 1H, NH-C=S). *Anal.* Calcd for C₁₆H₁₆N₄OS: 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 °C. IR (cm⁻¹): 3169 NH; 3047 CH arom; 2959, 1459 CH aliph; 1596 C=N; 1548 C-N; 1364 C=S. ¹H NMR (DMSO-d₆) δ : 4.48(d, *J*=5.6 Hz, 2H, CH₂); 7.19-7.57(m, 10H, arom); 9.96(s, 1H, NH); 10.25(s, 1H, NH-C=S). *Anal.* Calcd for C₁₅H₁₄N₄S: 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 °C. IR (cm⁻¹): 3149 NH; 3045 CH arom; 2949, 1457 CH aliph; 1589 C=N; 1510 C-N; 1347 C=S. ¹H NMR (DMSO-d₆) δ : 2.27(s, 3H, CH₃); 4.72(d, *J*=5.6 Hz, 2H, CH₂); 7.08-7.85(m, 9H, arom); 9.59(s, 1H, NH); 10.17(s, 1H, NH-C=S). *Anal.* Calcd for C₁₆H₁₆N₄S: 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 °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. ¹H NMR (DMSO-d₆) δ : 3.74(s, 3H, CH₃); 4.49(d, *J*=5.7 Hz, 2H, CH₂); 6.85-7.52(m, 9H, arom); 9.42(s, 1H, NH); 10.91(s, 1H, NH-C=S). *Anal.* Calcd for C₁₆H₁₆N₄OS: 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°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 °C. IR (cm⁻¹): 3427 NH; 2959 CH arom; 1597 C=N; 1548 C-N; 1368 C=S. ¹H NMR (DMSO-d₆) δ : 7.06-7.61(m, 10H, arom); 10.35(s, 1H, NH); 14.02(s, 1H, NH-C=S). *Anal.* Calcd for C₁₄H₁₂N₄S: 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 °C. IR (cm⁻¹): 3501 NH; 3097 CH arom; 2968, 1457 CH aliph; 1572 C=N; 1514 C-N; 1365 C=S. ¹H NMR (DMSO-d₆) δ : 2.50(s, 3H, CH₃); 7.09-7.51(m, 9H, arom); 10.24(s, 1H, NH); 13.97(s, 1H, NH-C=S). *Anal.* Calcd for C₁₅H₁₄N₄S: 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 °C. IR (cm⁻¹): 3504 NH; 3095 CH arom; 2958, 1452 CH aliph; 1594 C=N; 1546 C-N; 1367 C=S. ¹H NMR (DMSO-d₆) δ : 2.51(s, 3H, CH₃); 7.35-7.64(m, 9H, arom); 10.35(s, 1H, NH); 14.00(s, 1H, NH-C=S). *Anal.* Calcd for C₁₅H₁₄N₄S:

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 from dry 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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