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Research Article

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Synthesis of some new 5- substituted of 2-aminothiazoles: A new approach

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ABSTRACT

Halogenation of 2-aminothiazoles produces 2-amino-5-halothiazoles via an addition-elimination mechanism. Also the 2-amino-5-halothiazole can undergo nucleophilic substitution reaction in which halides is displaced by strong nucleophiles. In this study, was described synthesis of 5-substituted-2-aminothiazoles (5-aminogroup-2-amino-4-phenylthiazoles and bis(2-amino-4-substituted thiazole) sulfides), directly from 2-aminothiazoles via a two-step reaction (halogenation/nucleophilic substitution protocol). These syntheses were performed by three approaches (I: reaction of thiazoles and thiourea by $I_2/H_2O/EtOH$, II: reaction of thiazoles and thiourea or amine by $Br_2/NaHCO_3/DMF$, III: reaction of thiazoles and thiourea or amine using $CuBr_2$/Amine/CH_3CN). The main advantages of these approaches are that the reaction is fast, high yields, does not involve workup and isolation of halogenated intermediate.

Keywords: 2-aminothiazole, 5-bromo-2-aminothiazole, Bis(2-aminothiazole)sulfide, 5-amino-containing 2-amino-4-phenylthiazole

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INTRODUCTION

Thiazoles are significantly important heterocycles that represent interesting properties depending on the linked groups to the thiazole [1]. 2-aminothiazoles are a subclass of thiazole family that are of high interest due to their broad biological and non-biological activity (in example: as antibacterial [2], antifungal [3], antitubercular [4], anti-HIV [5], pesticidal [6], anti-inflammatory [7], antiprotozoal [8], antipyretic [9], antioxidative [10], analgesic [11], synthesis of polymers [12, 13], dyes [14, 15]). Due to the wide range of their application, 2-aminothiazoles viewed in terms of new synthetic methods and syntheses of new derivatives.

Some methods are reported for the synthesis of thiazoles involving condensation of substituted substrate before cyclization step [16, 17]. Also references are viewed in which 1,3-thiazole rings are entered into designed molecules by use of a mono-halothiazole in an organometal-catalyzed coupling procedure (in example: a Sonogashira [18], Heck [19], or Suzuki reaction [20]). Although halo-1,3-thiazoles are available, only a limited number are commercially access.

However, synthesis of 2-aminothiazole derivatives have problems such as harsh reaction conditions, low yields, difficult isolation procedures and the use of expensive catalysts etc [21, 22].

In continuation of our investigation on bis(2-aminothiazole)sulfide derivatives [12, 13], I report three efficient approaches for the synthesis of 5-amino-containing 2-amino-4-phenyl-thiazoles and bis(2-aminothiazole)sulfides,

directly from 2-aminothiazoles via a two-step reaction (halogenation/nucleophilic substitution protocol). These approaches were performed by merging and modifying the reported methods in literature [23, 24].

EXPERIMENTAL SECTION

All reactions were carried out in an efficient hood. The starting materials were purchased from Merck and Fluka chemical companies. Melting points were determined with a Branstead Electrothermal model 9200 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer RX 1 Fourier transform infrared spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 and Acetone-d_6 on Bruker Avance 300 MHz spectrometers. Elemental analyses were carried out by a Perkin Elmer 2400 series II CHN/O analyzer.

Method I: General procedure for Synthesis of 5,5'-bis(2-amino-4-substitued-1,3-thiazole)sulfide (BS_1-BS_6)
The 2-amino-thiazole derivative (2 mmol) and thiourea (3 mmol) were dissolved in 20 mL of water/ethanol (1:1). The mixture was heated on oil-bath with stirring at 60℃. The iodine (2.5 mmol) was added in small portions to the warm solution. The mixture was stirred for 3 hours to obtain the clear, reddish, solution. Then the solution became neutral by sodium hydroxide (10% w/w). The bis-[2-amino-thiazolyl] sulfide immediately separated in voluminous, pale yellow curds. The crude product was recrystallized from DMF/H_2O (1:1) to give corresponding pure products.

Method II: General procedure for Synthesis of (2-amino-4-substitued-1,3-thiazolyl)amine (AT_1-AT_6)
The 2-amino-thiazole derivative (2 mmol) and bromine (2 mmol) were dissolved in DMF (10 mL). The mixture was stirred for 3 h, at room temperature and then sodium hydrogen carbonate (4 mmol) and Na_2S (1 mmol) or amine (2 mmol; diamine: 1mmol) were added respectively. The mixture was heated on oil-bath at 70℃ for 3 hours. After cooling, the reaction mixture was poured in ice water and the precipitated solid was collected by filtration, washed with water and dried. The residue was purified by recrystallization (DMF/H_2O (1:1)) or column chromatography on silica gel, elution with 2:1 hexane–ethyl acetate (for amine derivatives).

Method III: General procedure for synthesis of (BS_1-BS_6) and (AT_1-AT_6)
2-Aminothiazole derivative (2 mmol) and $CuBr_2$ (2 mmol) were dissolved in acetonitrile (10 mL). This reaction mixture was stirred at 60 ^{0}C for 3h. Then was added Na_2S (1 mmol) or amine (2.5 mmol, diamine: 1 mmol) and stirred for 3 h. The reaction mixture was then evaporated and, the residue was washed with water and dried. Corresponding pure product was obtained by recrystallization or by column chromatography.

5,5´-bis(2-amino-4-methyl thiazole)sulfide (BS_1):
White solid, mp 191-192 °C; IR (KBr) ν: 3194, 3061, 2989, 1676, 1267, 808 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.15 (s, 6H), 7.13 (s, 4H, exchanged with D_2O) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 15.9, 109.0, 153.6, 168.5 ppm; Anal. Calcd for $C_8H_{10}N_4S_3$: C, 37.19; H, 3.90, N, 21.68. Found: C, 37.02; H, 3.83; N, 21.73.

5,5´-bis(2-amino-4-phenyl thiazole)sulfide (BS_2):
Yellowish solid, mp 178-179 °C; IR (KBr) ν: 3385, 3271, 3090, 1688, 1628, 1515, 1463, 1335, 697 cm^{-1} ; ^{1}H NMR (300 MHz, Acetone-d_6) δ: 7.0 (s, 4H, exchanged with D_2O), 7.28-7.30 (m, 6H), 7.63-7.66 (m, 4H) ppm; ^{13}C NMR (75 MHz, Acetone-d_6) δ:109.9, 128.4, 128.8, 129.8, 134.7, 159.3, 171.8 ppm; Anal. Calcd for $C_{18}H_{14}N_4S_3$: C, 56.62; H, 3.69; N, 14.65. Found: C, 56.53; H, 3.61; N, 14.73.

5,5´-bis(2-amino-4-(m-nitrophenyl) thiazole)sulfide (BS_3):
Orange solid, decomposed at 220 °C; IR (KBr) ν: 3418, 3305, 3182, 1631, 1530, 1350,681 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 753 (s, 4H), 7.58 (t, J = 7.8 Hz, 2H), 8.11 – 8.17 (m, 4H), 8.52 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 111.0, 122.63, 122.8, 129.5, 134.5, 135.2, 147.4, 150.2, 168.9 ppm; Anal. Calcd for $C_{16}H_{12}N_6O_4S_3$: C, 45.75; H, 2.56; N, 17.79. Found: C, 45.68; H, 2.49; N, 17.86**.**

5,5´-bis(2-amino-4-(p-nitrophenyl) thiazole)sulfide (BS_4):
Orange solid, decomposed at 300 °C; IR (KBr) ν: 3411, 3296, 3113, 1646, 1595, 1524, 1510, 1342, 1108, 839 cm^{-1} ; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.53 (s, 2H), 7.92 (d, J = 9.0 Hz), 8.13 (d, J = 9.0 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ:119.8, 130.2, 139.8, 147.8, 157.3, 170.3 ppm; Anal. Calcd for $C_{18}H_{12}N_6O_4S_3$: C, 45.75; H, 2.56; N, 17.79. Found: C, 45.63; H, 2.46; N, 17.89.

5,5´-bis(2-amino-4-(p-methoxyphenyl) thiazole)sulfide (BS_5):
Yellowish solid, mp 169 - 170 °C; IR (KBr) ν: 3453, 3280, 3095, 1625, 1606, 1520, 1243, 833 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.77 (s, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.55-7.61 (m, 4H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.0, 113.0, 126.3, 130.1, 157.6, 159.2, 170.4 ppm; Anal. Calcd for $C_{20}H_{18}N_4O_2S_3$: C, 54.28; H, 4.10; N, 12.66. Found: C, 54.23; H, 4.04; N, 12.75.

5,5´-bis(2-amino-4-(2-naphthyl) thiazole)sulfide (BS_6):
yellowish solid, mp 211-213 °C; IR (KBr) ν: 3456, 33360, 3263, 3099, 1622, 1527, 1493, 1491, 1322, 1293, 1198, 819 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ:7.38-7.54 (m, 4H), 7.81-7.88 (m, 8H), 8.08 (s, 2H); 8.57 (s, br, 4H, exchanged with D_2O) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 109.5, 123.4, 126.0, 126.6, 126.9, 127.1, 127.5, 127.7, 128.2, 128.9, 132.3, 132.7, 148.85 ppm; Anal. Calcd for $C_{26}H_{18}N_4S_3$: C, 64.70; H, 3.76; N, 11.61. Found: C, 64.65; H, 3.70; N, 11.73.

2-amino-5-N-morpholyl-4-phenyl-thiazole (AT_1):
Brownish, mp 204-206 °C with decomposition, yield 37%. IR spectrum (KBr), ν: 3383, 3279, 3241, 2964, 2909, 2857, 2819, 1626, 1531, 1326, 1042, 848, 693 cm^{-1}; ^1H NMR spectrum (DMSO-d_6) δ: 2.73 (t, *J* = 7.6 Hz, 4H), 3.72 (t, *J* = 7.6 Hz, 4H), 6.82 (s, 4H, exchanged with D_2O), 7.20-7.23 (t, J = 7.6 Hz, 1H), 7.46 (t, *J* =7.8 Hz, 2H), 8.1 (d, *J* = 7.8 Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 51.6, 70.2, 126.2, 127.9, 128.4, 136.5, 139.2, 163.8 ppm; Anal. Calcd for $C_{13}H_{15}N_3OS_3$: C, 59.74; H, 5.79; N, 11.08. Found: C, 59.68; H, 5.71; N, 11.16.

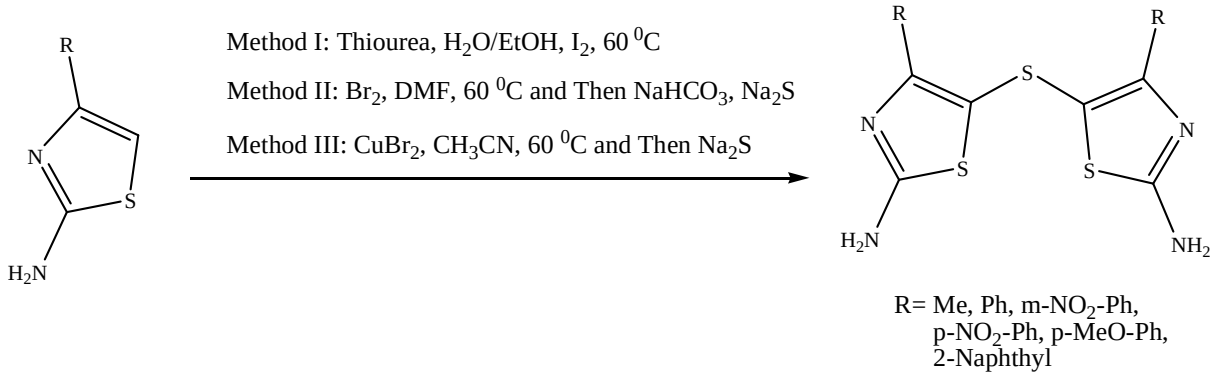
2-amino-5-N-piperdidinyl-4-phenylthaizole (AT_2):
Brownish solid, mp 213-215 °C; IR (KBr) ν: 3233, 3101, 2940, 1718, 1697, 1595, 1218 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.63-1.71 (m, 6H), 2.83 (s, br, 4H), 6.85 (s, 4H, exchanged with D_2O), 7.26 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 8.13 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 30.5, 30.9, 57.7, 124.2, 126.1, 128.3, 133.9, 137.2, 139.1, 163.2 ppm; Anal. Calcd for $C_{14}H_{17}N_3S$: C, 64.83; H, 6.61; N, 16.20. Found: C, 64.78; H, 6.69; N, 16.31.

N,N´-Bis(2-amino-4-phenylthiazolyl)hydrazine (AT_3):
Brownish, decomposed 105–107°C, yield 45%. IR (KBr) ν: 3443, 3375, 3230, 3172, 2857, 1623, 1508, 1336, 1069, 850, 695 cm^{-1}; ^1H NMR spectrum (300 MHz, DMSO-d_6) δ: 3.8 (s, br, 2H, exchanged with D_2O), 7.3 (m, 3H), 7.7 (m, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 127.1, 127.9, 129.3, 137.1, 138.0, 162.4 ppm; Anal. Calcd for $C_{18}H_{16}N_6S_2$: C, 56.82; H, 4.24; N, 22.09. Found: C, 56.75; H, 4.18; N, 22.17.

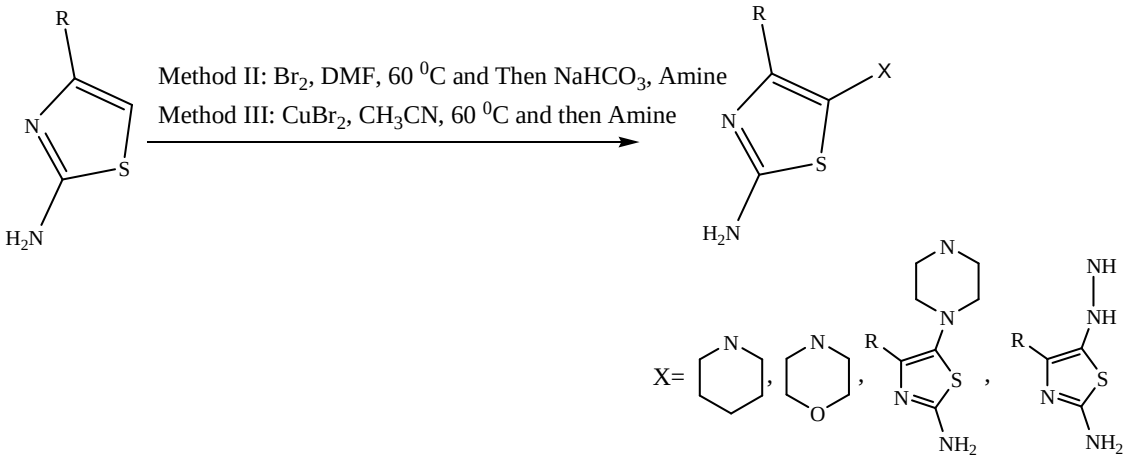
N,N´-Bis(2-amino-4-phenylthiazolyl)piperazine (AT_4):
Brownish solid, decomposed at 118 °C; IR (KBr) ν: 3463, 3354, 3286, 31117, 1656, 1635, 1532, 1209, 696 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.87 (s, 8H), 6.85 (s, 4H, exchanged with D_2O), 7.21 (t, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 4H), 8.06 (d, *J* = 7.8 Hz, 4H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ: 54.9, 126.6, 127.4, 128.0, 134.7, 136.9, 138.7, 162.3; ppm; Anal. Calcd for $C_{22}H_{22}N_6S_2$: C, 60.80; H, 5.10; N, 19.34. Found: C, 60.73; H, 5.01; N, 19.48.

RESULTS AND DISCUSSION

In the initial experiments, the synthesis of 5,5'-bis(2-amino-4-phenyl-1,3-thiaolze)sulfide (**BS_1**) was carried out using a procedure described by Woodbridge et al. [23] (reaction of thiourea, 2-amino-4-phenylthiazole in the presence I_2). **BS_1** was obtained in 61% yield (**Method I**; Scheme 1). In the synthesis of amino derivatives, (insertion of morpholine on C5), and the targeted 5-amino-containing 2-aminothiazole (**AT_1)** was not detectable in **method I**. Thus the other reaction was designed, using bromine in DMF, to obtain bromothiazole and then sodium hydrogen carbonate and amine were added to produce **AT_1** (**method II**; Scheme II**)**. In this method, **AT_1** was obtain, but with a low yield. Thus, amino-4-phenyl-1,3-thiazole was reacted with $CuBr_2$ (according to method specified by Siméon et al for the synthesis 2-amino-5-halo-thiazole [24]), then the resulted reaction mixture was treated with morpholine in the same pot, to afford **AT_1** in high yield (**method III**; Scheme I). Lastly, the reaction based on **method I, II, III** (scheme I & II) were performed for other derivatives and the results are summarized in Table 1 & 2,



Scheme 1 Synthesis of 5,5´-bis(2-aminothiazole)sulfide derivatives



Scheme 2 Synthesis of 5-aminocontaining-2-aminothiazole derivatives

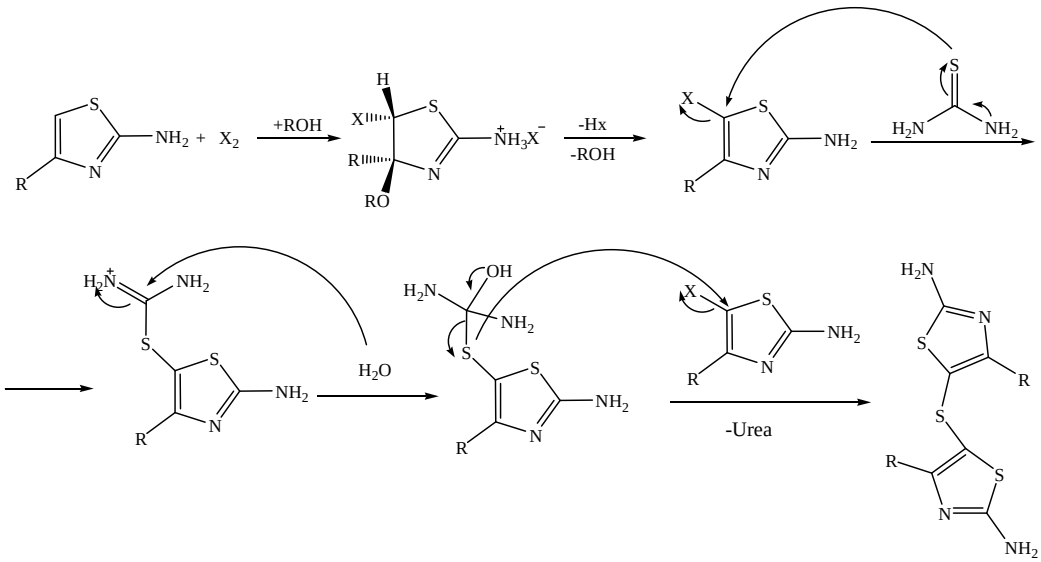
Table 1 synthesis of 5,5´-bis(2-aminothiazole)sulfide derivatives

Entry	R	Product	Yield% (Method I)	Yield% (Method II)	Yield% (Method III)
1	Methyl	BS_1	61	43	73
2	Phenyl	BS_2	65	47	74
3	m-NO_2-phenyl	BS_3	81	51	85
4	p-NO_2-phenyl	BS_4	70	50	81
5	p-MeO-phenyl	BS_5	57	48	67
6	2-naphthyl	BS_6	47	35	65

Table 2 5-amino-containing 2-aminothiazole derivatives

Entry	R	Amine	Product	Yield% (method I)	Yield% (method II)	Yield% (method III)
1	Phenyl	piperidine	AT_1	0	47	63
2	Phenyl	Morpholine	AT_2	0	51	67
3	Phenyl	Hydrazine	AT_3	0	42	58
4	Phenyl	Piperazine	AT_4	0	64	78

Although synthesis of bisulfide derivatives based on **method I**, was successful, but the amine derivatives was not detectable in this method. From a mechanismic point of view (scheme 3) [25], it can be due to, the formation of HBr in the iodization step of 2-aminothiazol (in-situ formation and consumption 5-iodo-2-aminothiazole). In the presence stronger amine (as morpholine) than 2-aminothiazole, the H acidic produces ammonium salt of stronger amine and the reaction does not proceed. If the reactions media become non-acidic, the intermediate would not form and therefore, the reaction stops.



Scheme 3 Proposed mechanism for synthesis bis-sulfides in manner method I

Thus **method II** was used to btain 2-amino-5-bromo-4-phenyl-thiazole, more stable than corresponding iodine derivative, and the solution was neutral with $NaHCO_3$. 2-Amino-5-bromo4-phenyl-thiazole is stable in this media. Then was added Na_2S or amine to produce targeted molecules in low yield.

To minimize these difficulties, I was performed a reaction using $CuBr_2$ instead I_2 or Br_2, according to represented method in ref. 24 to obtain bromothiazoles. Then, nucleophilic substitution reactions of resulted bromothaizoles were produced desired thiazole in good yield. Several 4-substituted-2-aminothaizoles underwent the reaction to give the corresponding bis-sulfide in excellent yields. In the case of amination only 2-amino-4-phenylthiazole was run, the yields of product were satisfy. The experimental procedure was very simple and convenient (Table 1 & 2).

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