Synthesis of substituted 2-amino-1,3-thiazine-6-thiones

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The reaction of thiourea with 1-acyl-2-bromoacetylenes in AcOH in the presence of $BF_3 \cdot Et_2O$ affords 2-amino-4-phenyl(2-thienyl)-1,3-thiazine-6-thiones in high yields.

Key words: 1-acyl-2-bromoacetylenes; thiourea; intramolecular cyclization; 2-amino-4-phenyl-1,3-thiazine-6-thione, 2-amino-4-(2-thienyl)-1,3-thiazine-6-thione.

It is known that *p*-methoxybenzoyl-, *p*-chlorobenzoyl-, and benzoylphenylacetylenes react with thiourea in MeOH to give a mixture of *Z,Z*- and *E,Z*-isomers of aroyl vinyl sulfides.[1] The reaction of ethynyl phenyl ketone with thiourea in 2*N* HCl yields *S*-(2-benzoylvinyl)isothiuronium chloride. When stored in water-alcohol solution, the latter undergoes cyclization into 2-imino-4-phenyl-1,3-thiazine hydrochloride.[2] Aroylphenylacetylenes react with thiourea in EtOH at 60 °C in the presence of sodium ethoxide to form 4,6-diarylpyrimidine-2(1*H*)-thiones[3].

It is also known that the reaction of substituted thioureas with 1-benzoyl-2-bromoacetylene at 20 °C in various solvents results in *N*-substituted 4-benzoyl-2-(*R*-imino)-1,3-thiazolium bromides.[4]

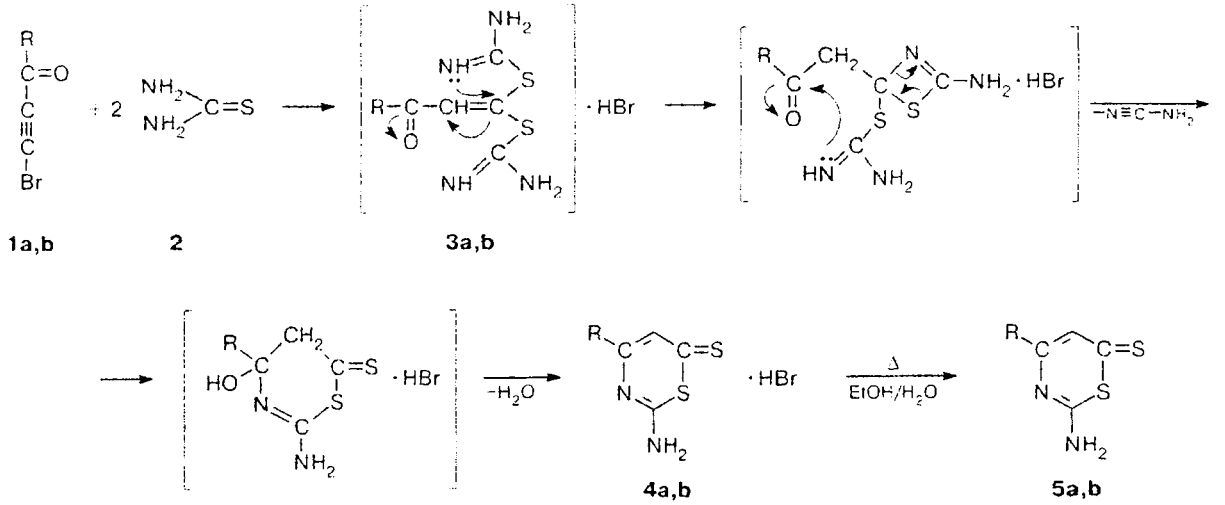
We found that the reaction of 1-acyl-2-bromoacetylenes **1a,b** with thiourea (**2**) in the ratio of 1 : 2 in glacial AcOH in the presence of $BF_3 \cdot Et_2O$ at 40 °C affords 1,3-thiazine-6-thione hydrobromides **4a,b** in high yields (Scheme 1). Recrystallization of the latter from a water-alcohol mixture gives free bases **5a,b**.

Apparently, the reaction mechanism includes the formation of intermediate α-oxoketene mercaptals **3a,b**, whose intramolecular cyclization in the presence of $BF_3 \cdot Et_2O$ results—with elimination of cyanamide and water—in substituted 2-amino-1,3-thiazine-6-thiones **4a,b**.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer (400.1 and 100.51 MHz, respectively). IR spectra were recorded on a Specord 75IR spectrometer (in pellets with KBr). Melting points were determined on a NAGEMA hot stage (GDR). Commercial solvents were purified according to the known procedures.[5] Commercial $BF_3 \cdot Et_2O$ was distilled at 125 °C in a flow of nitrogen dried over conc. H_2SO_4. Diethyl ether was treated with a 1% aqueous solution of

Scheme 1



R = Ph (**a**); 2-thienyl (**b**)

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$KMnO_4$ to remove peroxides, dried over $CaCl_2$, and distilled over sodium metal.

1-Benzoyl-2-bromoacetylene (1a) was prepared by brominating 1-phenylprop-2-yn-1-ol synthesized as described in Ref. 6. Bromine (1.65 mL) was slowly added with stirring to crushed ice (15 g) and a 40% aqueous solution of NaOH (7.5 mL). Stirring was continued until bromine dissolution was completed. To the resulting sodium hypobromite a solution of 1-phenylprop-2-yn-1-ol (3.96 g, 0.03 mol) in 30 mL of ether was added, and the mixture was stirred at 20 °C for 3 h and decomposed with a 10% aqueous solution of ammonium chloride. The organic material was extracted with ether. The extract was dried with $MgSO_4$ and filtered. 3-Bromo-1-phenylprop-2-yn-1-ol obtained was oxidized *in situ* with MnO_2 at 20 °C for 1 h to give ketone **(1a)** (4.8 g, 76%), m.p. 90—91 °C (*cf.* Ref. 5: m.p. 94—95 °C).

1-Bromo-2-(2-thenoyl)acetylene (1b) was synthesized in a similar way by brominating 1-(2-thienyl)prop-2-yn-1-ol[6] (4.14 g, 0.03 mol), according to the known procedure.[7] Yield 4.8 g (75%), m.p. 83 °C.

2-Amino-4-phenyl-1,3-thiazine-6-thione hydrobromide (4a). 1-Benzoyl-2-bromoacetylene **(1a)** (2.09 g, 10 mmol) and thiourea **(2)** (1.52 g, 20 mmol) were added to a solution of $BF_3 \cdot Et_2O$ (1.42 g, 10 mmol) in 30 mL of glacial AcOH. The reaction mixture was stirred at 40 °C for 1 h and cooled to ~20 °C. The precipitate that formed was filtered off, washed with 10 mL of glacial AcOH and 40 mL of anhydrous ether, and dried *in vacuo* to give orange needles, yield 2.5 g (83%), m.p. 228—230 °C (from glacial AcOH). IR (KBr), ν/cm^{-1}: 2900—3300 (br., NH_3^+); 1630, 1600, 1535 (C=C, C=N, δ NH). ^{13}C NMR (DMSO-d_6), δ: 197.1 (C=S); 170.11 (C(2)); 159.58 (C(4)); 137.36, 134.62, 131.86, 130.48 (Ph); 114.31 (C=H). Found (%): C, 40.02; H, 3.12; Br, 26.64; N, 9.14; S, 21.27. $C_{10}H_9BrN_2S_2$. Calculated (%): C, 39.88; H, 3.01; Br, 26.53; N, 9.30; S, 21.29.

2-Amino-4-phenyl-1,3-thiazine-6-thione (5a). Compound **4a** (1 g) was dissolved with heating in a mixture of 95% EtOH (30 mL) and water (70 mL), refluxed for 30 min, and cooled to 20 °C. The brown crystals that formed were filtered off, washed with 40 mL of cold water, and dried *in vacuo* over $CaCl_2$. Yield 0.68 g (93%), m.p. 198—200 °C. IR (KBr), ν/cm^{-1}: 3080, 3275 (NH_2); 1640, 1540, 1460 (C=C, C=N, bend. NH). ^1H NMR (DMSO-d_6), δ: 7.28 (s, 1 H, CH=); 7.45—8.07 (m, 5 H, Ph); 9.01 (s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6), δ: 197.89 (C=S); 169.76 (C(2)); 158.72 (C(4)); 137.20, 131.37, 128.68, 127.79 (Ph); 114.07 (C=H). Found (%): C, 54.55; H, 3.95; N, 12.67; S, 29.17. $C_{10}H_8N_2S_2$. Calculated (%): C, 54.52; H, 3.66; N, 12.72; S, 29.10.

By analogy with compound **4a**, **2-amino-4-(2-thienyl)-1,3-thiazine-6-thione hydrobromide (4b)** was obtained as an amorphous brown powder from 1-bromo-2-(2-thenoyl)acetylene **(1b)** (2.16 g, 10 mmol) and thiourea **(2)** (1.52 g, 20 mmol). Yield 2.1 g (68%), m.p. 222—224 °C (from glacial AcOH). IR (KBr), ν/cm^{-1}: 2800—3200 (br., NH_3^+); 1630, 1575, 1400 (C=C, C=N, bend. NH). Found (%): C, 31.04; H, 2.32; Br, 26.58; N, 9.31; S, 31.01. $C_8H_7BrN_2S_3$. Calculated (%): C, 31.27; H, 2.30; Br, 26.01; N, 9.12; S, 31.30.

By analogy with compound **5a**, **2-amino-4-(2-thienyl)-1,3-thiazine-6-thione (5b)** was obtained as dark red needles from hydrobromide **4b**. Yield 0.63 g (85%), m.p. 215—217 °C. IR (KBr), ν/cm^{-1}: 3125, 3275 (NH_2); 1625, 1540, 1460 (C=C, C=N, bend. NH). ^1H NMR (DMSO-d_6), δ: 7.35 (s, 1 H, CH=); 7.22—8.07 (m, 4 H, C_4H_3S, CH=); 8.97 (s, 2 H, NH_2). Found (%): C, 42.25; H, 2.45; N, 12.38; S, 42.13. $C_8H_6N_2S_3$. Calculated (%): C, 42.46; H, 2.67; N, 12.38; S, 42.50.

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