

**Cu-CATALYZED “ON-WATER” REARRANGEMENT OF 2-AMINOBENZOTHAZOLES TO PHENOTHIAZINES. REACTIONS OF SUBSTITUTED 2-AMINOTHIAZOLES AND 2-AMINO-3-BENZYL BENZOTHAZOL-3-IUM BROMIDE WITH 1,2-DIBROMOBENZENES AND TETRACHLOROETHYLENE**

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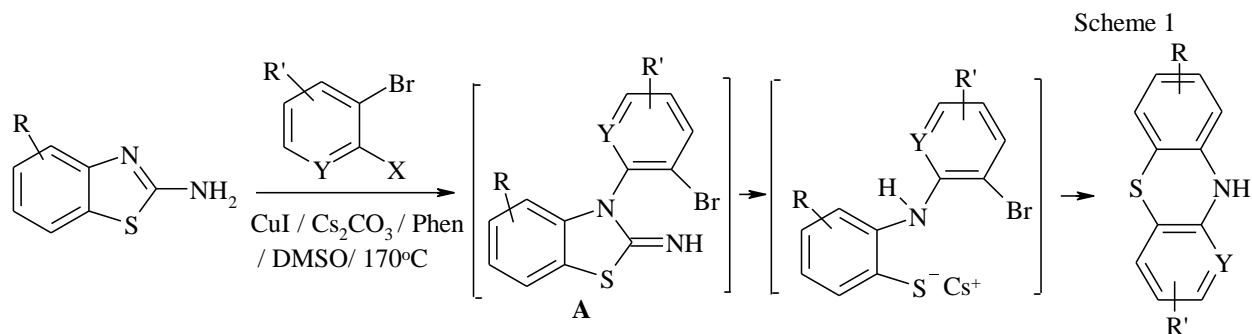
**ABSTRACT:**

Novel “on-water” catalytic system (1-bromo-2-iodobenzene, CuI (10 mol.%) / proline (20 mol %) / Adogen 464 (methyltrialkylammonium chloride) (100 mg) / KOH / H<sub>2</sub>O) for the rearrangement of 2-aminobenzothiazoles to phenothiazines was developed. It has been found that substituted 2-aminothiazoles and 2-amino-3-benzylbenzothiazol-3-ium bromide in the presence of 1,2-dibromobenzenes or tetrachloroethylene undergo rearrangement to 1,4-benzothiazines.

**Keywords:** Cu-catalysis, „on-water” synthesis, N-arylation, phenothiazines, 1,4-benzothiazines

**INTRODUCTION**

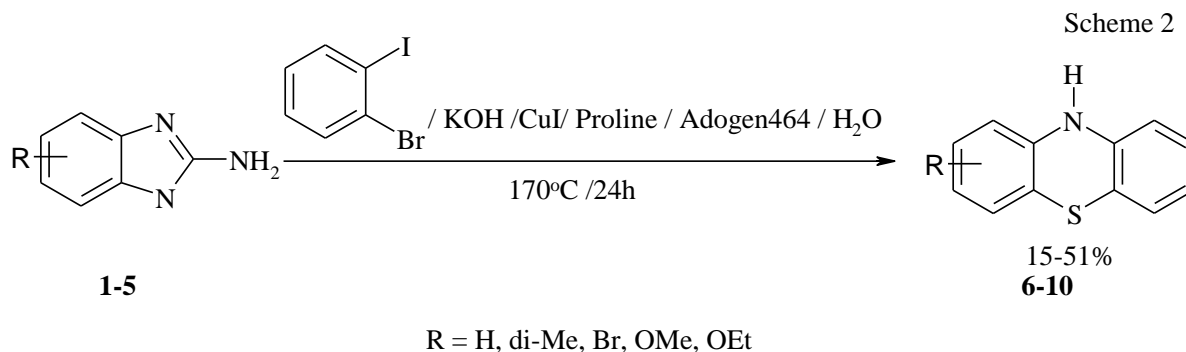
Phenothiazines<sup>I</sup> classically were prepared by interaction of diphenylamine hydrochloride with sodium thiosulfate<sup>II</sup>. These compounds were also prepared from 2-phenylaminobenzoic acids and iodine in the presence of sulfur<sup>III</sup>, diaryl amines and iodine / sulfur<sup>IV, V</sup>, 2-azidodiarylsulfides / decahydronaphthalene / I<sub>2</sub> / pyridine (then Cu / quinoline)<sup>VI</sup> and 2-nitrodiarylsulfides and triethyl phosphite<sup>VII</sup>. Two Cu-catalyzed methods for the synthesis of phenothiazines in the systems 2-amino-2'-bromodiarylsulfides CuI / K<sub>2</sub>CO<sub>3</sub> / L-proline / methoxymethyl ester<sup>VIII</sup> and 2-aminomercaptanes / 1,2-dibromobenzenes / CuI / K<sub>2</sub>CO<sub>3</sub> / DMSO<sup>IX</sup> have been developed. Recently we described novel synthesis of phenothiazines by Cu-catalyzed rearrangement of 2-aminobenzothiazoles in the presence of 1,2-dibromobenzenes (or 2,3-dibromopyridine) in the system CuI / 1,10-phenanthroline (Phen) / Cs<sub>2</sub>CO<sub>3</sub> / DMSO (Scheme 1)<sup>X</sup>.



However, in the above article only synthesis of phenothiazines by Cu-catalyzed rearrangement of 2-aminobenzothiazoles to phenothiazines was described. Investigation of products obtained on the treatment of 2-aminothiazoles, 2-amino-5-alkylbenzothiazolium bromides with 1,2-dihalobenzenes or tetrachloroethylene was not investigated till now. Beside this, novel „on-water” method for the preparation of phenothiazines from 2-aminobenzothiazoles was presented for the first time.

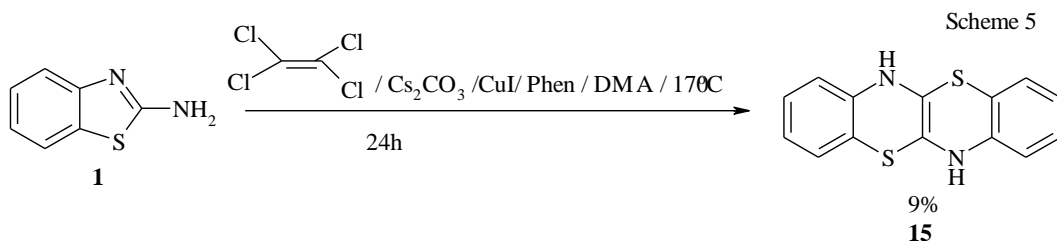
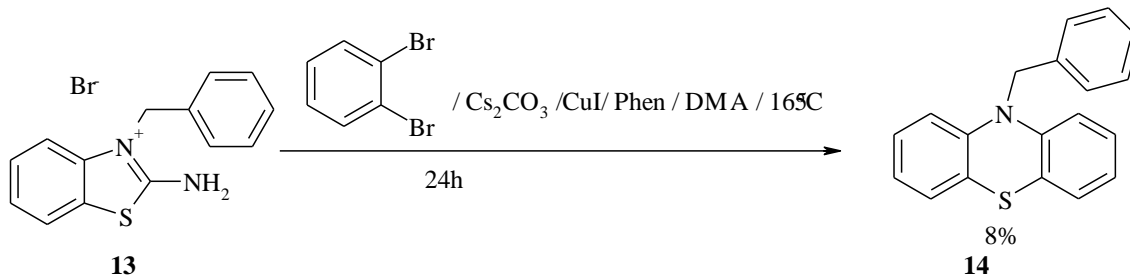
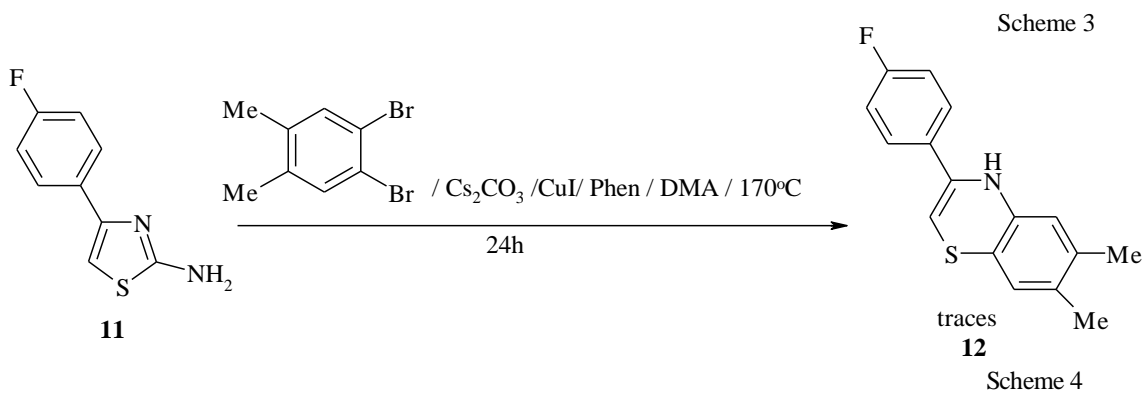
## RESULTS AND DISCUSSION

We have elaborated novel catalytic system for the preparation of phenothiazines **6-10** in the water. Thus, the interaction of 2-aminobenzothiazoles **1-5** with 1-bromo-2-iodobenzene in the system CuI (10 mol.%) / proline (20 mol %) / Adogen 464 (methyltrialkylammonium chloride) (100 mg) / KOH / H<sub>2</sub>O leads to phenothiazines **6-10** in 15-51% yield (Scheme 2). Adogen 464 as the phase transfer agent or cationic surfactant was widely used in the organic synthesis. However, Adogen 464 as additive in the Cu-catalyzed reactions in water was recently demonstrated in the synthesis of imidazothiazoles<sup>XI</sup>. Interestingly, that in the absence of Adogen 464 only trace amounts of phenothiazine **6** was obtained. Moreover, workup of the reaction mixtures in the cases **6-10** was very simple – products were isolated by simple filtration or extraction with ethyl acetate, followed by column chromatography (eluent hexane: EtOAc 1:4 or 1:2), to get the analytical samples.



The rearrangement of 4-substituted-2-aminothiazoles and 2-amino-3-benzylbenzothiazol-3-ium bromide was not investigated to now and therefore is the second aim

of work. Thus, the treatment of 4-(4-fluorophenyl)thiazol-2-ylamine (**11**) with 4,5-dimethyl-1,2-dibromobenzene in the system CuI / Cs<sub>2</sub>CO<sub>3</sub> / Phen / DMA at 170°C leads only to trace amounts of 3-(4-fluorophenyl)-6,7-dimethyl-4H-benzo[1,4]thiazine (**12**) registered by GH-MS and <sup>1</sup>H NMR data (Scheme 3). The reaction of 2-amino-3-benzylbenzothiazol-3-ium bromide (**13**) with 1,2-dibromobenzene in the above system leads to 10-benzyl-10H-phenothiazine **14** in 8% yield (See Experimental) (Scheme 4). The treatment of 2-aminobenzothiazole **1** with tetrachloroethylene in the system CuI / Cs<sub>2</sub>CO<sub>3</sub> / Phen / DMA at 170°C afforded thiazine derivative **15** in 9% yield (Scheme 5).



## EXPERIMENTAL

<sup>1</sup>H spectra were registered on Varian Mercury BB instrument (400 MHz) in CDCl<sub>3</sub>. The residual proton signal of the solvent ( $\delta = 7.26$  ppm) was used as the reference. Electron impact ionization mass spectra were recorded on Agilent Technologies 5975C MSD detector at 70 eV. 2-Aminobenzothiazoles, CuI, 1,10-phenanthroline, 2-aminobenzothiazoles, dimethylacetamide (Acros) and extra dry DMSO and Adogen464 (Aldrich) were used without purification. 4-(4-Fluorophenyl)-thiazol-2-ylamine (**11**) was prepared according procedure<sup>XII</sup>. 2-Amino-5-benzylbenzothiazolium bromide (**13**) were prepared in 59% yield by refluxing of equimolar amounts of 2-aminobenzothiazole and benzyl bromide in EtOAc.

**General procedure for the Cu-catalyzed synthesis of phenothiazines 6-10 from 2-aminobenzothiazoles 1-5 in water.** Solid KOH (0.22 g, 4 mmol) was added to the solution of 2-aminobenzothiazoles **1-5** (1 mmol), 1-bromo-2-iodobenzene (0.34g, 1.2 mmol), CuI (0.038 g, 0.2 mmol), proline (0.020g, 0.2 mmol) and Adogen 464 (100 mg) in water (2 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at 170°C for 24 h under argon. The product removed by filtration or extraction with ethyl acetate, followed by column chromatography (eluent hexane: EtOAc 1:4 or 1:2), to get analytical sample.

Spectroscopic and physical properties of 10H-phenothiazine (**6**) (yield 51%)<sup>XIII</sup>, 2,3-dimethyl-10H-phenothiazine (**8**) (yield 42%)<sup>VIII</sup> and 3-methoxy-10H-phenothiazine (**9**) (yield 40%)<sup>XV</sup> are identical with those described in the literature.

**2-Bromo-10H-phenothiazine (7)**<sup>XIV</sup>. Yield 15%. M.p. 180-182°C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ, ppm: 5.77 (1H, bs, NH), 6.53 and 6.96 (2H, both d, J = 6 Hz, 4-H and 5-H), 6.70 (1H, s, 2-H), 6.79-7.03 (4H, m, C<sub>6</sub>H<sub>4</sub>). GC-MS: 278.0 (M<sup>+</sup>, 98), 277.0 (100), 245.0 (10), 198.0 (99), 171.0 (31), 154.1 (42), 139.3 (21), 127.0 (12), 98.6 (33), 85.5 (13), 63.0 (16).

**3-Ethoxy-10H-phenothiazine (10)**<sup>XVI</sup>. Yield 41%. M.p. 148-150°C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ, ppm: 1.36 (3H, t, J = 7.6 Hz, CH<sub>3</sub>), 3.98 (2H, q, J = 7.6 Hz, CH<sub>2</sub>), 6.56-6.65 and 6.98-7.02 (7H, both m, aromatic protons). GC-MS: 243.1 (M<sup>+</sup>, 100), 214.0 (97), 186.1 (57), 154.0 (11), 115.0 (11).

**Cu-catalyzed synthesis of 1-benzyl-10H-phenothiazine (14) from 2-amino-3-benzylbenzothiazol-3-ium bromide (13).** Dry Cs<sub>2</sub>CO<sub>3</sub> (0.977 g, 3 mmol) was added to the solution of 2-amino-3-benzylbenzothiazol-3-ium bromide (**13**) (0.32g, 1.0 mmol), 1,2-dibromobenzene (0.12 ml, 1 mmol), CuI (0.038g, 0.2 mmol) and 1,10-phenanthroline (Phen) (0.040g, 0.2 mmol) in dry DMA (4 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at 165°C for 24 h under argon. The solvent was removed under reduced pressure and crude residue was chromatographed on silica using toluene (100%) as eluent. Spectroscopic and physical properties of 1-benzyl-10H-phenothiazine (**14**) are identical with those described in the literature<sup>XVII</sup>.

**Cu-catalyzed reaction of 2-aminobenzothiazole with tetrachloroethylene.** Dry Cs<sub>2</sub>CO<sub>3</sub> (0.977 g, 3 mmol) was added to the solution of 2-aminobenzothiazole (**1**) (0.15g, 1.0 mmol), tetrachloroethylene (0.051 ml, 0.5 mmol), CuI (0.038g, 0.2 mmol) and 1,10-phenanthroline (Phen) (0.040g, 0.2 mmol) in dry DMA (4 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at 170°C for 24 h under argon. The solvent was removed under reduced pressure and crude residue was chromatographed on silica using hexane : EtOAc (5:1) as eluent. Yield 9% of compound **15** as yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ, ppm: 7.33-7.59, 7.84-7.88, 7.96-8.04 and 8.13-8.17 (8H, all m, C<sub>6</sub>H<sub>4</sub>). GC-MS: 270 (M<sup>+</sup>, 10), 268.0 (100), 242.0 (6), 134.0 (11), 108.0 (22), 82.0 (11), 69.0 (18).

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