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Cu-CATALYZED "ON-WATER" REARRANGEMENT OF 2-AMINOBENZOTHIAZOLES TO PHENOTHIAZINES. REACTIONS OF SUBSTITUTED 2-AMINOTHIAZOLES AND 2-AMINO-3-BENZYLBENZOTHIAZOL-3-IUM BROMIDE WITH 1,2-DIBROMOBENZENES AND TETRACHLOROETHYLENE

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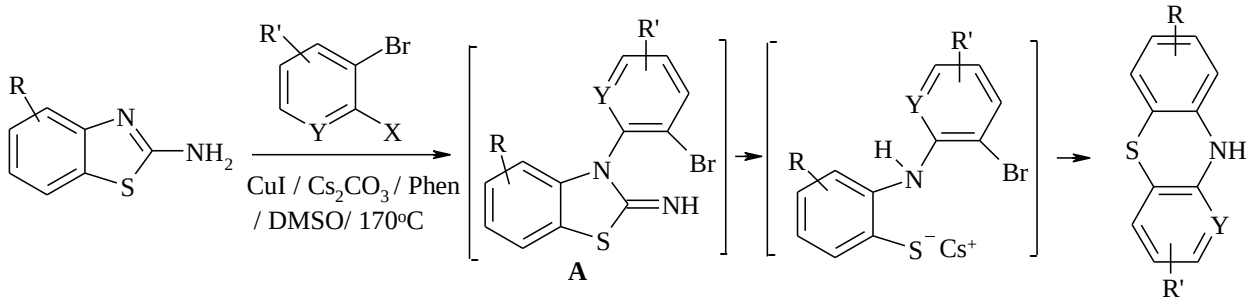
ABSTRACT:
Novel "on-water" catalytic system (1-bromo-2-iodobenzene, CuI (10 mol.%) / proline (20 mol %) / Adogen 464 (methyltrialkylammonium chloride) (100 mg) / KOH / H_2O) for the rearrangement of 2-aminobenzothiazoles to phenothiazines was developed. It have been found that substituted 2-aminothiazoles 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 [I] classically were prepared by interaction of diphenylamine hydrochloride with sodium thiosulfate [II]. These compounds were also prepared from 2-phenylaminobenzoic acids and iodine in the presence of sulfur [III], diaryl amines and iodine / sulfur [IV, V], 2-azidodiarylsulfides / decahydonaphthalene / I_2 / pyridine (then Cu / quinoline) [VI] and 2-nitrodiarylsulfides and triethyl phosphite [VII]. Two Cu-catalyzed methods for the synthesis of phenothiazines in the systems 2-amino-2'-bromodiarylsulfides CuI / K_2CO_3 / L-proline / methoxymethyl ester [VIII] and 2-aminomercaptanes / 1,2-dibromobenzenes / CuI / K_2CO_3 / DMSO [IX] have been developed. Recently we described novel synthesis of phenothiazines by Cu-catalyzed rearrangement of 2-aminobenzothazoles in the presence of 1,2-dibromobenzenes (or 2,3-dibromopyridine) in the system CuI/ 1,10-phenanthroline (Phen) / Cs_2CO_3 / DMSO (Scheme 1) [X].

Scheme 1

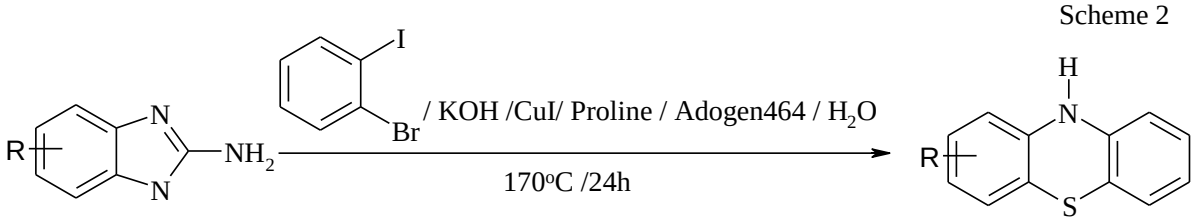


However, in the above article only synthesis of phenothiazines by Cu-catalyzed rearrangement of 2-aminobenzothiazoles to phenothiazines was described. Investigation of products obtained on the treatment of 2-aminothiazoles, 2-amino-5-alkylbenzothiazolium bromides with 1,2-dihalobenzenes or tetrachloroethylene 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_2O 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 [XI]. 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.

Scheme 2



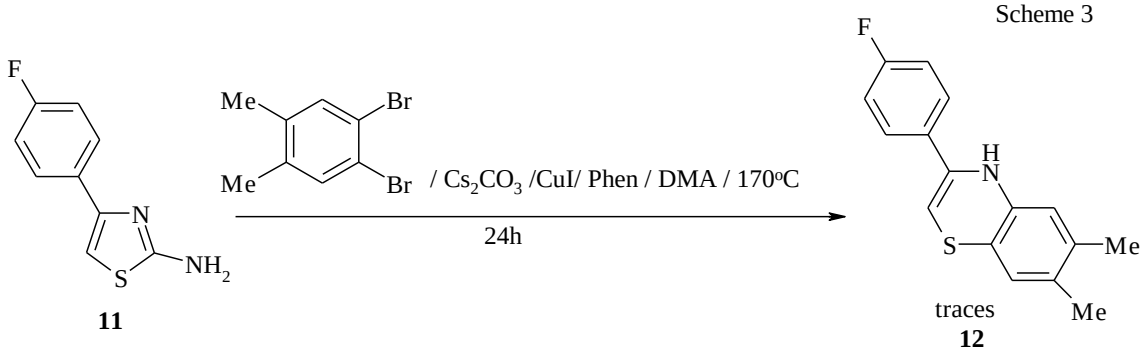
1-5 **6-10**

R = H, di-Me, Br, OMe, OEt

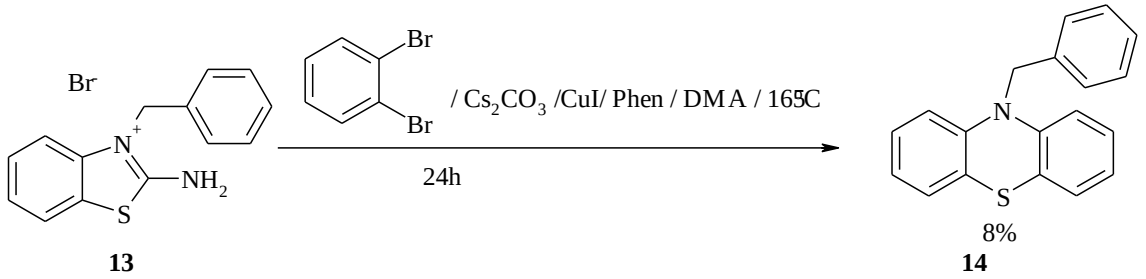
The rearrangement of 4-substituted-2-aminothiazoles and 2-amino-3-benzylbenzothiazol-3-ium bromide was not investigated to now and therefore is the second aim

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_2CO_3 / 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 ^{1}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_2CO_3 / Phen / DMA at 170°C afforded thiazine derivative **15** in 9% yield (Scheme 5).

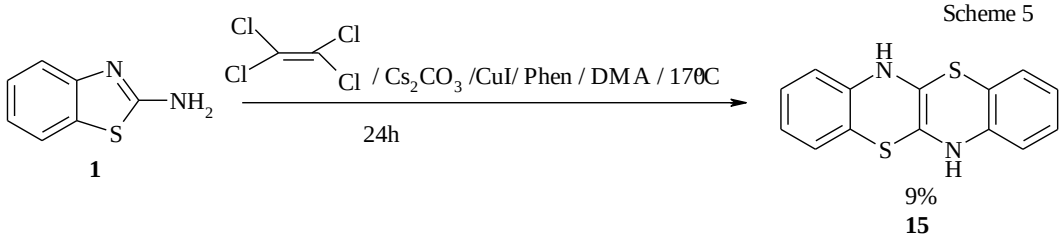
Scheme 3



Scheme 4



Scheme 5



EXPERIMENTAL

^{1}H spectra were registered on Varian Mercury BB instrument (400 MHz) in $CDCl_3$ The residual proton signal of the solvent (δ =7.26 pm) 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 [XII]. 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-aminothiazoles 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^{o}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%) [XIII], 2,3-dimethyl-10H-phenothiazine (**8**) (yield 42%) [VIII] and 3-methoxy-10H-phenothiazine (**9**) (yield 40%) [XV] are identical with those described in the literature.

2-Bromo-10H-phenothiazine (7) [XIV]. Yield 15%. M.p. 180-182^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) 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_6H_4). GC-MS: 278.0 (M^+, 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**) [XVI]. Yield 41%. M.p. 148-150^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 1.36 (3H, t, J = 7.6 Hz, CH_3), 3.98 (2H, q, J = 7.6 Hz, CH_2), 6.56-6.65 and 6.98-7.02 (7H, both m, aromatic protons). GC-MS: 243.1 (M^+, 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-benzybenzolthiazol-3-ium bromide (13).** Dry Cs_2CO_3 (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^{o}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 [XVII].

Cu-catalyzed reaction of 2-aminobenzothiazole with tetrachloroethylene. Dry Cs_2CO_3 (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^{o}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. ^{1}H NMR (400 MHz, $CDCl_3$) δ, ppm: 7.33-7.59, 7.84-7.88, 7.96-8.04 and 8.13-8.17 (8H, all m, C_6H_4). GC-MS: 270 (M^+, 10), 268.0 (100), 242.0 (6), 134.0 (11), 108.0 (22), 82.0 (11), 69.0 (18).

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