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SCOPE AND MECHANISM OF Cu-CATALYZED REACTIONS OF 2-AMINOBENZOTHIAZOLE AND 1-BENZYL-2-AMINOBENZOIMIDAZOLE WITH 1-BROMO-2-IODOBENZENE

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ABSTRACT:
Selectivity of synthesis of phenothiazine or benzoimidazo[2,1-*b*]benzothiazole by Cu-catalyzed reaction of 2-aminobenzothiazoles with 1-bromo-2-iodobenzene was strongly influenced by added base. The reaction of 2-aminobenzothiazole with 1-bromo-2-iodobenzene in the presence of inorganic bases (KOH and Cs_2CO_3) selectively leads to phenothiazine in 52 or 57% yields, correspondingly. Similar Cu-catalyzed reaction in the presence of DBU leads to a mixture of phenothiazine (26%) and benzoimidazo[2,1-*b*]benzothiazole (47%). 1-Benzyl-2-aminobenzoimidazole and 1-bromo-2-iodobenzene in the systems CuI/ Cs_2CO_3 / Phen/ DMA and CuI / Proline/ KOH / Adogen464/ H_2O at 160^oC selectively leads to 5-benzylbenzoimidazo[2,1-b]benzoimidazole.

Keywords: Cu-catalysis, 1-bromo-2-iodobenzene, phenothiazine, benzoimidazo[2,1-*b*]benzothiazole, 5-benzylbenzoimidazo[2,1-*b*]benzoimidazole

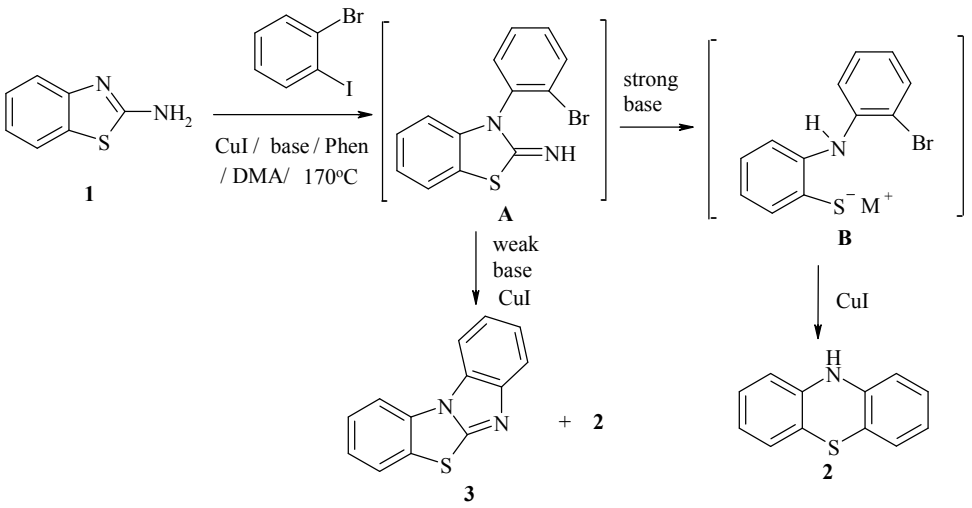
INTRODUCTION

Imidazothiazoles and related compounds are of great interest as biologically active compounds [I,II]. Recently we described two novel Cu-catalytic systems for the preparation of derivatives of benzoimidazo[2,1-*b*]benzothiazole from corresponding 2-mercaptobenzoimidazoles and 1,2-dibromobenzenes or pyridines [III, IV]. Phenothiazines [V] classically were prepared by interaction of Ph_2NH with sodium thiosulfate [VI]. Recently three Cu-catalyzed methods for the synthesis of phenothiazines in the systems 2-amino-2'-bromodiarylsulfides/ CuI / K_2CO_3 / L-proline / methoxymethyl ester [VII], 2-aminomercaptanes / 1,2-dibromobenzenes / CuI / K_2CO_3 / DMSO [VIII] and 2-aminobenzothiazoles/ 1,2-dibromobenzenes/ CuI/ 1,10-phenanthroline (Phen) / Cs_2CO_3 / DMSO [IX] or CuI/ proline / Adogen464/ H_2O [X] have been developed.

RESULTS AND DISCUSSION

However, it also was founded that selectivity of synthesis of phenothiazines by Cu-catalyzed rearrangement of 2-aminobenzothiazoles to phenothiazines was strongly influenced by added base. In the present article the influence of different bases in the Cu-catalyzed reaction of 2-aminobenzothiazole **1** with 1-bromo-2-iodobenzene in DMA will be presented for the first time (for reaction conditions see Experimental). Interestingly, that the reaction of amine **1**

with 1-bromo-2-iodobenzene in the presence of inorganic bases (KOH and Cs_2CO_3) selectively leads to phenothiazine (**2**) in 52 or 57% yields, correspondingly (Table 1). However, using DBU as base in the Cu-catalyzed reaction of compound **1** with 1-bromo-2-iodobenzene affords benzoimidazo[2,1-*b*]benzothiazole **3** as main product in 47% yield. Phenothiazine (**2**) was isolated as minor product in 26% yield. Using urotropine, DABCO, Et_3N and pyridine as bases in the above reaction was correspondingly less effective in the synthesis of compounds **2** and **3**.

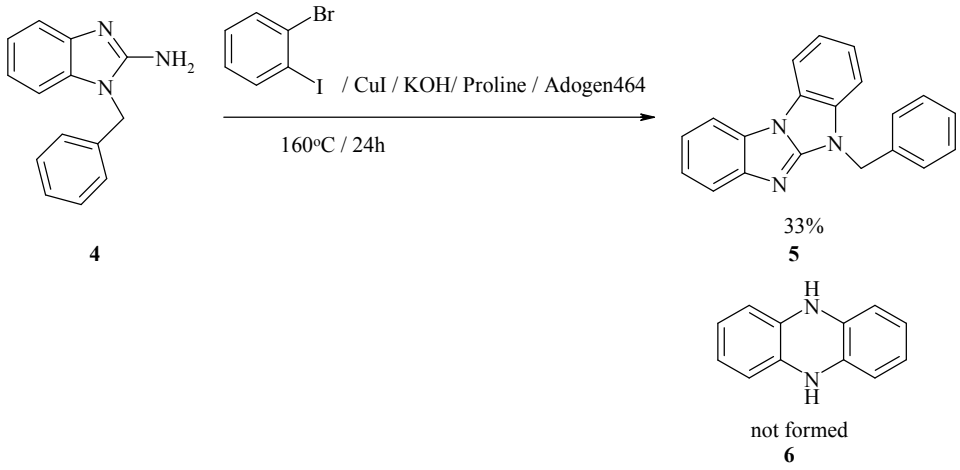


The mechanism of formation of phenothiazine (**2**) and benzoimidazo[2,1-*b*]benzothiazole (**3**) in the presence of different bases including Cu-catalyzed C-3 arylation of 2-aminobenzothiazole leading to the intermediate **A.** The next step of reaction was strongly influenced by added base. The presence of mineral bases KOH or Cs_2CO_3 afforded ring opening intermediate **B**. Intermediate **B** then readily undergoes selective Cu-catalyzed cyclization to phenothiazine **2**. If the reaction of amine **1** with 1-bromo-2-iodobenzene was carried out in the presence of organic base (for example, DBU) the main product was corresponding benzoimidazo[2,1-*b*]benzothiazole (**3)** as the result of direct intramolecular arylation of imine group in the intermediate **A**.

Table 1. Cu-catalyzed reactions of 2-aminobenzothiazole 1 with 1-bromo-2-iodobenzene in the presence of different bases. Synthesis of phenothiazine (**2**) and/or benzoimidazo[2,1-*b*]benzothiazole (**3**).

Base	Yield of phenothiazine (**2**), % [IX]	Yield of benzoimidazo[2,1-*b*]benzothiazole (**3**), [III]	Starting (recovered) 2-aminobenzothiazole (**1**) , %
KOH	52	0	0
Cs_2CO_3	**57**	0	0
Et_3N	Traces	6	42
urotropine	15	16	Traces
DABCO	9	4	6
DBU	26	**47**	0
Pyridine	Traces	Traces	6

Interestingly, that the reactions of 1-substituted-2-aminobenzoimidazoles with 1,2-dihalobenzenes was not studied till now. Therefore, we tried the reaction of 1-benzyl-2-aminobenzoimidazole (**4**) with 1-bromo-2-iodobenzene in two catalytic systems ((Method A) CuI/ Cs_2CO_3 / Phen/ DMA and (Method B) CuI / Proline/ KOH / Adogen464/ H_2O at 160°C with the aim to investigate structure obtained products in comparison with 2-aminobenzothiazole rearrangement. Surprisingly, that in the both cases single product and a novel heterocyclic system – 5-benzylbenzoimidazo[2,1-b]benzoimidazole (**5**) in 27% (Method A) and 33% (Method B) yields, correspondingly, formed. Using of organic bases in the synthesis of compound **5** was considerably less effective. Interestingly, that the formation of 5,10-dihydrophenazine (**6**) does not occurred.



4 **5** **6**

EXPERIMENAL

^1H and ^{13}C NMR spectra were registered on Varian Mercury BB instrument (400 and 100 MHz, respectively) 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. Melting points were detected on Boetius aparatos equipped with visual detector PHMH 05. The progress of the reactions was monitored by TLC Silica gel 60 F_{254} aluminium sheets using hexane: ethyl acetate in the different mixtures as eluent. 2-Aminobenzothiazole, 2-aminobenzoimidazole, CuI, 1,10-phenanthroline and extra dry dimethylacetamide (DMA) (Acros), Adogen464 (Aldrich) were used without purification. 1-Benzyl-2-aminobenzoimidazole (**4**) was prepared by benzylation of 2-aminobenzoimidazole as described in article [XI].

General procedure for the Cu-catalyzed reactions of 2-aminobenzothiazole 1 with 1-bromo-2-iodobenzene in the presence of different bases. Synthesis of phenothiazine (2) [IX] **and/or benzoimidazo[2,1-*b*]benzothiazole (3)** [III]. Base (4 mmol) was added to the solution of 2-aminobenzothiazole (**1**) (0.15g, 1.0 mmol) and 1-bromo-2-iodobenzene (0.153 ml, 1.2 mmol), CuI (0.038g, 0.2 mmol) and 1,10-phenanthroline (phen) (0.040g, 0.2 mmol) in dry DMA (8 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 : ethyl acetate (4:1 to 2:1) as eluent. The results see in Table 1.

Cu-catalyzed synthesis of 5-benzylbenzoimidazo[2,1-*b*]benzoimidazole (5) from 1-benzyl-2-aminobenzoimidazole (4). KOH (0.34 g, 6 mmol) was added to the solution of 1-benzyl-2-aminobenzoimidazole (**4**) (0.223 g, 1.0 mmol) and 1-bromo-2-iodobenzene (0.154 ml, 1.2 mmol), CuI (0.038g, 0.2 mmol), proline (0.023g, 0.2 mmol) and Adogen464 (100 mg)

in H_2O (2 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at 160°C for 24 h under argon. The product was extracted with ethyl acetate, dried (Na_2SO_4), solvent was removed under reduced pressure and crude residue was chromatographed on silica using hexane: EtOAc (1:1) as eluent. Yield 0.097g (33%) of compound **5** as brown crystals with m.p.71-73°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.39 (s, 2H, CH_2); 7.11-7.36, 7.63-7.65 and 7.70-7.75 (all m, 13H, Ph and C_6H_4). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ (ppm): 46.88, 110.02, 110.05, 110.44, 118.41, 119.76, 121.13, 122.88, 122.97, 125.28, 127.53, 127.95, 128.62, 128.78, 135.21, 135.47, 147.22, 153.66. Mass-spectrum, *m/z* (I_{rel}, %): 297.1 (M^+, 85), 206.1 (26), 91.0 (100), 65.0 (10). Found, %: C 80.05; H 4.99; N 13.97. $C_{20}H_{15}N_3$. Calculated, %: C 80.78; H 5.08; N 14.13.

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