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REGIOSELECTIVITY IN THE Cu-CATALYZED SYNTHESIS OF SUBSTITUTED BENZO- AND PYRIDO-FUSED IMIDAZO[2,1-*b*]THIAZOLES AND PYRIMIDO[2,1-*b*]BENZOTHIAZOL-4-ONE

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ABSTRACT:
A simple one-flask method for the selective preparation of benzo- and pyrido-fused imidazo[2,1-*b*]thiazoles and pyrimido[2,1-*b*]benzothiazol-4-one from corresponding thiones and 1-bromo-2-iodobenzenes or 2,3-dibromopyridines in the bicatalytic system solid KOH / CuI / 1,10-phenanthroline / Bu_4NBr / DMF has been developed. Reaction of 1,3-dihydrobenzimidazol-2-thione with 3-bromo-4-iodotoluene in the above system leads to 5-methylbenzimidazo[2,1-*b*]benzothiazole as single cyclization product by selective stepwise S- and N-arylation tandem reaction.

Keywords: copper catalysis, 1,3-dihydrobenzimidazol-2-thione, phase transfer catalysis, imidazo[2,1-*b*]thiazoles, pyrimido[2,1-*b*]benzothiazol-4-one

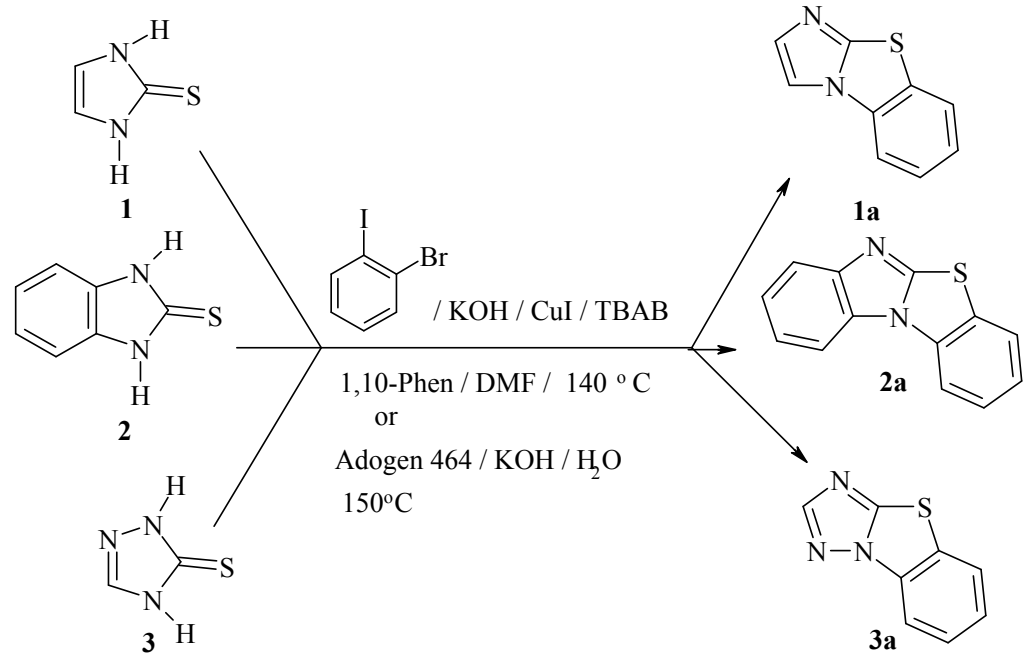
INTRODUCTION

Imidazothiazoles and related compounds are of great interest as biologically active compounds.[I-VI] Imidazo[2,1-*b*]benzothiazole and its benzo analogs usually were obtained in the systems 2-aminobenzothiazole / chloroacetaldehyde/ 1-butanol,[VII] 1-(3-chlorophenyl)-2-mercaptoimidazole / $NaNH_2$ / NH_3,[VIII] 2-iodobenzothiazole / 2-iodoaniline / CuI / 1,10-phenanthroline / Cs_2CO_3 / xylene, [IX] 2-mercaptobenzimidazole / 1-bromo-3,4-dicyano-2-nitrobenzene / K_2CO_3 [X] or by photolysis of 1-(2-benzothiazolyl)benzotriazole [XI]. 4*H*-Pyrimido[2,1-*b*]benzothiazol-4-ones were prepared by multistep reaction starting from 2-aminobenzothiazoles [XII-XIV].
Recently we have elaborated two novel and simple Cu-catalyzed methods for the preparation of derivatives of imidazo[2,1-*b*]thiazoles **1a** and **2a** and benzo[4,5]thiazolo[3,2-*b*][1,2,4]triazole (**3a**) from corresponding thiones **1-3** (Scheme 1) [XY]. The main aim of present work is investigation of regioselectivity of formation of benzo- and pyrido-fused imidazo[2,1-*b*]thiazoles and pyrimido[2,1-*b*]benzothiazol-4-one.

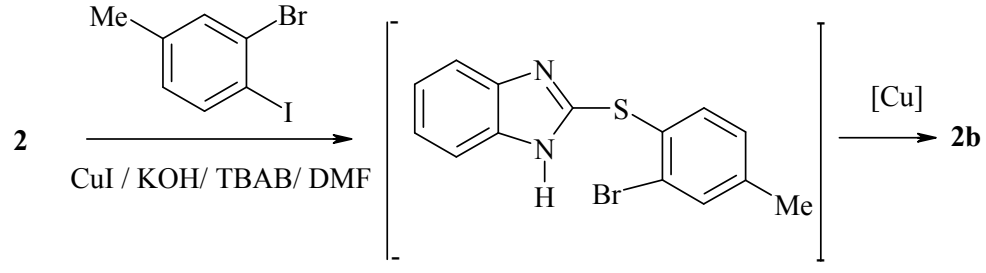
RESULTS AND DISCUSSION

Synthesis of benzo- and pyrido-fused imidazo[2,1-*b*]thiazoles and pyrimido[2,1-*b*]benzothiazol-4-one were carried out from corresponding thiones **2** and **4** by one flask stepwise S,N-diarylation reaction in the bicatalytic system 4-bromo-3-iodotoluene / solid KOH / CuI / 1,10-Phen (1,10-

phenanthroline) / TBAB / DMF (Scheme 1). Interestingly, that the reaction of thione **2** with 4-bromo-3-iodotoluene in the system solid KOH / CuI / TBAB / 1,10-Phen / DMF afforded single cyclization product 9-methylbenzimidazo[2,1-*b*]benzothiazole (**2b**) in 32 % yield. It means that iodide in the 3-bromo-4-iodotoluene selectively reacts with S-nucleophilic part of the thione **2** forming intermediate **A**, which undergo Cu-catalyzed cyclization to product **2b** (Scheme 2).



Scheme 1

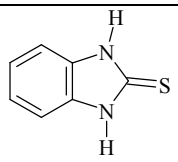
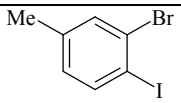
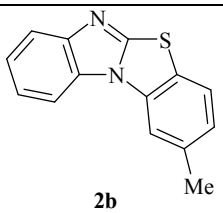
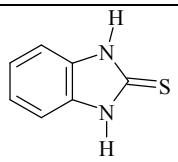
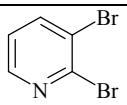
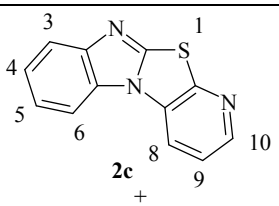
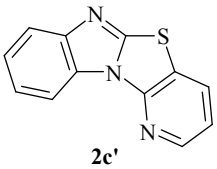
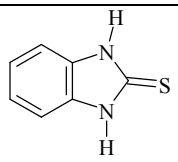
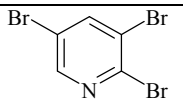
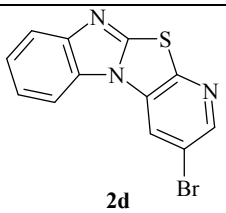
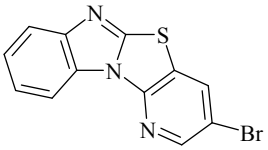
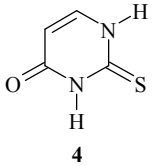
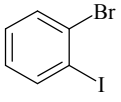
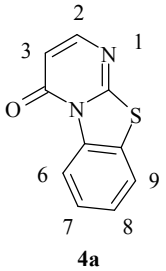


Scheme 2

Reaction of thione **2** with 2,3-dibromopyridine in the system solid KOH / CuI / 1,1-Phen / TBAB / DMF leads to a mixture of unstable products **2c** (9% yield) and **2c'** (5% yield). Interestingly, that the interaction of thione **2** with 2,3,5-tribromopyridine afforded selectively 9-bromopyrido[3'2':3,5]thiazolo[3,2-*a*]benzimidazole (**2d**) in 49% yield (see Table 1). In means, that in this case with S-nucleophilic part of thione **2** at first selectively reacted bromide in the position 2 in pyridine ring. The second step of reaction is substitution of bromide in the position 3 in pyridine ring with N-nucleophilic part of thione **2** leading to product **2d**.

Similarly was prepared pyrimido[2,1-*b*]benzothiazol-4-one (**4a**) from corresponding thione **4** and 1-bromo-2-iodobenzene.

Table 1. Synthesis of imidazo[2,1-*b*]thiazoles and pyrimido[2,1-*b*]benzothiazol-4-one from corresponding thiones and 1-bromo-2-iodobenzenes or 2,3-dibromopyridines in the system solid KOH / CuI / 1,1-Phen / TBAB / DMF

Starting thione	Halide	Product	Reaction time, h	Yield, %
 **2**		 **2b**	19	32
 **2**		 **2c** +  **2c'**	27	9 (**2c**) [a] 5 (**2c'**) [a, b]
 **2**		 **2d** +  **2d'**	19	49 (**2d**) traces (**2d'**) [b]
 **4**		 **4a**	19	11

[a] Compounds **2c** and **2c'** are unstable and therefore were registered by ^{1}H NMR and LC-MS only.
[b] Compound **2c'** and **2d'** was registered by LC-MS spectra only.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were registered on Varian Mercury BB 400 MHz in $CDCl_3$. Mass-spectra were recorded on Alliance Waters 2695 instrument with Full scan POS NEG 16 detector. Thiones **2** and **4,** 1-bromo-2-iodobenzene (all Acros), copper (I) iodide, Bu_4NBr, 1,10-phenanthroline (Reahim) and dimethylformamide (extra dry, over molecular sieves, Acros) were used without purification. Melting points were detected on Boetius apparatus equipped with visual detector PHMH 05. HR-MS spectra were performed on Micromass Q-TOF Micro quadrupole-time of flight high resolution mass spectrometer. Leucine enkephalin was used as internal lock mass for accurate mass calculation. 2,3-Dibromopyridine and 2,3,5-tribromo-pyridine were obtained from 2-amino-3-bromopyridine in the system $NaNO_2$ / HBr / H_2O.

General procedure for the synthesis of fused thiazoles 2b-d, 4a. Solid KOH (0.39 g, 6 mmol) was added to the solution of thiones **2** and **4** (1.5 mmol) and 1-bromo-2-iodobenzenes or 2,3-dibromopyridines (1.5 mmol), CuI (0.057g, 0.3 mmol) and TBAB (0.097 g, 0.3 mmol), 1,10-phenanthroline (0.3 mmol) in dry DMF (10 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at 140 ^{o}C (TLC-control, see Table 1) under argon. The solvent was removed under reduced pressure and crude residue was chromatographed on silica using hexane : ethyl acetate (from 4:1 to 0:1) as eluent.

9-Methylbenzimidazo[2,1-*b*]benzothiazole (**2b**). M.p. 140-142^{o}C. LC-MS, 239 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.47 (3H, s, Me); 7.30 (1H, d, *J* = 8.4 Hz, H-10); 7.33-7.42 (m, total 2H, H-4 and H-5); 7.50 (s, 1H, H-8); 7.78 (d, 1H, *J* = 8.4 Hz, H-11); 7.81 and 7.90 (2H, both m, H-3 and H-6). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ (ppm): 21.3 (Me); 110.4; 111.9; 119.4; 121.7; 123.3; 124.4; 127.4; 129.0; 130.4; 131.0; 134.4; 148.2; 155.3. Found, *m/z* (EI): 239.0648 [M+H]. $C_{14}H_{11}N_2S$. Calculated, *m/z*: 239.0643.

Pyrido[3'2':3,5]thiazolo[3,2-*a*]benzimidazole (2c). M.p.199^{o}C (dec). LC-MS 226 (M^++1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39-7.51 and 7.85-7.91 (5H, both m, H-3, H-4, H-5, H-6 and H-9); 8.11 (1H, *J* = 8 Hz, H-8); 8.46 (1H, d, *J* = 4 Hz, H-10);

9-Bromopyrido[3'2':3,5]thiazolo[3,2-*a*]benzimidazole (2d). M.p. 198-199^{o}C. LC-MS 305 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37-7.46 (2H, m, 4-H and 5-H); 7.80-7.84 (2H, m, 3-H and 6-H); 8.18 (1H, d, *J* = 2.0 Hz, 8-H); 8.52 (1H, d, *J* = 2.0 Hz, 10-H). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ (ppm): 110.3; 117.7; 120.0; 120.8; 122.8; 124.4; 129.3; 130.0; 145.8; 147.0; 150.8; 153.2. Found, *m/z* (EI): 303.9527 $[M]^+$. $C_{12}H_6BrN_3S$. Calculated, *m/z*: 303.9544.

Pyrimido[2,1-*b*]benzothiazol-4-one (4a).[XII-XIV] M.p. 164-165^{o}C. LC-MS, 203 (M^++1). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.40 (1H, d, *J* = 8.0 Hz, H-3); 7.94 (1H, d, *J* = 8.0 Hz, H-2); 7.50 (m, 2H, H-7 and H-8); 7.68 (1H, d, *J* = 7.2 Hz, H-9); 9.08 (1H, d, *J* = 6.8 Hz, H-6). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ (ppm): 109.4 (C-3); 120.2; 121.7; 124.2; 126.9; 127.2; 136.0; 151.8 (C-2); 161.0; 162.2. Found, *m/z* (EI): 203.0270 [M+H]. $C_{10}H_7N_2OS$. Calculated, *m/z*: 203.0279.

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