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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 / Bu₄NBr / 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. Imidazo[2,1-b]benzothiazole and its benzo analogs usually were obtained in the systems 2-aminobenzothiazole / chloroacetaldehyde / 1-butanol, 1-(3-chlorophenyl)-2-mercaptoimidazole / NaNH₂ / NH₃, 2-iodobenzothiazole / 2-idoaniline / CuI / 1,10-phenanthroline / Cs₂CO₃ / xylene, 2-mercaptobenzimidazole / 1-bromo-3,4-dicyano-2-nitrobenzene / K₂CO₃ or by photolysis of 1-(2-benzothiazolyl)benzotriazole. 4H-Pyrimido[2,1-b]benzothiazol-4-ones were prepared by multistep reaction starting from 2-aminobenzothiazoles.

Recently we have elaborated two novel and simple Cu-catalyzed methods for the preparation of derivatives of imidazo[2,1-b]thiazoles and benzo[4,5]thiazolo[3,2-b][1,2,4]triazole (3a) from corresponding thiones 1-3 (Scheme 1). 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...
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](image1)

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.

![Scheme 2](image2)
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

<table>
<thead>
<tr>
<th>Starting thione</th>
<th>Halide</th>
<th>Product</th>
<th>Reaction time, h</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="" alt="thione2" /></td>
<td><img src="" alt="halide1" /></td>
<td><img src="" alt="product2b" /></td>
<td>19</td>
<td>32</td>
</tr>
<tr>
<td><img src="" alt="thione2" /></td>
<td><img src="" alt="halide2" /></td>
<td><img src="" alt="product2c" /></td>
<td>27</td>
<td>9 (2c) ^a, 5 (2c') ^a, b</td>
</tr>
<tr>
<td><img src="" alt="thione2" /></td>
<td><img src="" alt="halide3" /></td>
<td><img src="" alt="product2c" /> + <img src="" alt="product2c'" /></td>
<td>19</td>
<td>49 (2d) traces (2d') ^b</td>
</tr>
<tr>
<td><img src="" alt="thione4" /></td>
<td><img src="" alt="halide4" /></td>
<td><img src="" alt="product4a" /></td>
<td>19</td>
<td>11</td>
</tr>
</tbody>
</table>

^a Compounds 2c and 2c' are unstable and therefore were registered by ^1H 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$_4$NBr, 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-tribromopyridine were obtained from 2-amino-3-bromopyridine in the system NaNO$_2$ / HBr / H$_2$O.

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-iodobenzene or 2,3-dibromopyridines (1.5 mmol), CuI (0.057 g, 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°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°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); 7.78 (d, 1H, $J = 8.4$ Hz, H-11); 7.81 and 7.90 (2H, both m, HM3 and HM6). $^{13}$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$_2$S. Calculated, m/z: 239.0643.

Pyrido[3'2':3,5]thiazolo[3,2-a]benzimidazole (2c). M.p. 199°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, HM3, HM4, HM5, HM6 and HM9); 8.11 (1H, $J = 8$ Hz, HM8); 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°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$_6$BrN$_3$S. Calculated, m/z: 303.9544.

Pyrimido[2,1-b]benzothiazol-4-one (4a). M.p. 164-165°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$_7$N$_2$OS. Calculated, m/z: 203.0279.
REFERENCES


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