PALLADIUM-CATALYZED ROUTE TO NOVEL FIVE- AND SIX-CYCLIC HETEROCYCLIC SYSTEMS CONTAINING THIAZOLE, IMIDAZOLE AND OXEPINE RINGS

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ABSTRACT

Novel and simple two step catalytic method for the preparation of novel five- and six-cyclic heterocyclic systems containing thiazole, imidazole and oxepine rings from 3-chloromethylbenzo[4,5]imidazo[2,1-b]thiazole and o-bromobenzyl alcohols or 2-bromo-3-hydroxymethylpyridine was described.

Keywords: Palladium catalyst, coupling, 3-chloromethylbenzo[4,5]imidazo[2,1-b]thiazole, phase transfer catalysis, five- and six-cyclic heterocyclic systems

INTRODUCTION

Seven-membered heterocyclic motifs are usually present in the wide range of biologically active molecules 1. Wide range of recent chemical review literature is dedicated to synthesis and transformation of seven membered rings 2-5. The most important and updated development in palladium-catalyzed synthesis of different heterocyclic compounds including oxepine ring using intramolecular Heck type reaction was recently highlighted in some reviews 6-9. Beside this synthesis of oxepines and their benzo derivatives by ring closing metathesis were well documented 10. Among these works some recent publications were connected with benzoxepine ring preparation by palladium 11,12 or osmium 13 catalysis. However, there is no data in the literature connected to synthesis of different types of fused thiazolooxepines, thiazolobenzoxepines and related compounds and therefore is the main aim of the present work. Beside this, amount of methods for the preparation of large-membered ring systems by intramolecular Heck type cyclisation is limited and yields of products in such reactions usually are not high. Our interest in polycyclic compounds containing imidazothiazole and related fragments is also connected with a wide range of biological activity of imidazothiazole heterocyclic systems 14,15.

RESULTS AND DISCUSSION

Herein we report a novel and simple palladium-catalyzed method for the preparation of novel five- and six-cyclic heterocyclic systems containing thiazole, imidazole and oxepine rings from 3-chloromethylbenzo[4,5]imidazo[2,1-b]thiazole (I) and o-bromobenzyl alcohols or 2-bromo-3-hydroxymethylpyridine. The synthesis of compounds 5-7 was carried out using two step method. The first step included selective O-alkylation of o-bromobenzyl alcohols or 2-
bromo-3-hydroxymethylpyridine in the phase transfer catalytic system 3-chloromethylbenzo[4,5]imidazo[2,1-b]thiazole (1) / solid KOH / 18-crown-6 / PhMe (Scheme 1). Substituted 3-[2-bromophenyl(or pyridyl)methoxymethyl]benzo[4,5]imidazo[2,1-b]thiazoles (2-4) were isolated by column chromatography in 50-77 % yields.

\[
\begin{array}{ccc}
\text{Cl} & \text{Br} & \text{X} \\
\text{N} & \text{S} & \text{O} \\
\end{array}
\xrightarrow{\text{KOH / 18-crown-6 / PhMe}}
\begin{array}{ccc}
\text{Br} & \text{X} & \text{R} \\
\text{N} & \text{S} & \text{O} \\
\end{array}
\xrightarrow{\text{Pd(OAc)}_2/\text{Xantphos}}
\begin{array}{ccc}
\text{X} & \text{R} \\
\text{N} & \text{S} & \text{Cl} \\
\end{array}
\xrightarrow{\text{Cs_2CO_3 / Ag_2CO_3 / PhMe}}
\begin{array}{ccc}
\text{X} & \text{R} \\
\text{N} & \text{S} & \text{Cl} \\
\end{array}
\]

X= CH, N; R= H; RR = O(CH_2)_2

The second step of reaction is Pd(0)-catalyzed cyclization of 3-[2-bromophenyl(or pyridyl)methoxymethyl]benzo[4,5]imidazo[2,1-b]thiazoles 2-4. Our previously experiments showed that catalytic system bromide 2-4 / solid dry Cs_2CO_3 / Pd(OAc)_2 / Xantphos / Ag_2CO_3 in dry toluene was the best for the preparation of oxadiazepines 5-7. Products 5-7 were isolated in 11-21 % yields (see Table 1 and Experimental section).

Structure of compound 5 was confirmed by X-Ray structural data (see Experimental section). Fig. 1 illustrates a perspective view of the molecule 5, showing the thermal ellipsoids and the atom-numbering scheme followed in the text. In the seven-membered cycle of O14–C13–C4–C5–C14–C16–C15 the atoms of C4, C5, C14 and C16 lie in one plane. The deviations of C15, O14 and C13 atoms from this plane are equal –0.245(5), 0.790(4) and 0.375(5) Å, respectively. The other cycles in the molecule are planar.

In the crystal structure there are π-π stacking interactions between two molecules of 5 connected by a center of inversion. This fact leads to short intermolecular contacts: C5···C8 (1.379(5) Å) and C2···C12 (1.397(5) Å).

Figure 1. ORTEP molecular structure of the compound 5.
Table 1. Synthesis of substituted 3-(2-bromophenyl(or pyridyl)methoxymethyl)benzo[4,5]imidazo[2,1-b]thiazoles (2-4) and five- and six-cyclic heterocycles 5-7.

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield, %</th>
<th>Melting point, °C</th>
<th>$^1$H NMR, δ, ppm</th>
<th>$^{13}$C NMR, δ, ppm</th>
<th>LC-MS</th>
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<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>77</td>
<td>151-152</td>
<td>4.74 and 4.93 (both s, 4H, CH$_2$), 6.75 (s, 1H, thiazole proton), 7.15 (t, 1H, J = 8.0 Hz, aryl), 7.22-7.27 and 7.34-7.43 (both m, aryl), 7.53, 7.78 and 7.87 (all d, 3H, J = 8.0 Hz, aryl)</td>
<td>64.62, 71.48, 109.46, 111.98, 119.04, 121.04, 122.91, 123.44, 127.50, 129.41, 129.45, 129.95, 130.01, 132.63, 136.26, 148.41, 156.93</td>
<td>375 (M$^+$+2)</td>
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<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>50</td>
<td>188-189</td>
<td>4.20 (m, 4H, CH$_2$CH$_2$), 4.62 and 4.88 (both s, 4H, CH$_2$), 6.73 (s, 1H, thiazole proton), 6.90 and 7.04 (both s, 2H, aryl), 7.27 and 7.37 (both t, 2H, J 7.2 Hz, aryl), 7.77 and 7.86 (both d, 2H, aryl)</td>
<td>64.17, 64.31, 71.08, 109.32, 112.05, 113.55, 118.40, 118.97, 120.94, 121.04, 123.40, 128.96, 129.94, 130.14, 142.98, 143.95, 148.38, 156.90</td>
<td>433 (M$^+$+2)</td>
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<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>63</td>
<td>75-77</td>
<td>4.71 and 4.98 (both s, 4H, CH$_2$), 6.79 (s, 1H, thiazole proton), 7.14-7.39 (m, 3H, aryl and pyridine), 7.69-7.86 (m, 3H, aryl and</td>
<td>65.07, 70.07, 109.92, 111.71, 119.21, 121.15, 122.90, 123.56, 129.52, 129.86, 134.03, 136.93, 141.65, 148.41, 149.10, 156.86</td>
<td>374 (M$^+$)</td>
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<td>4.84 and 5.51 (both s, 4H, CH₂), 7.23-7.31 (m, 3H, aryl), 7.34-7.42 (m, 3H, aryl), 7.55 (t, 2H, J = 7.2 Hz, aryl), 7.79 (d, 1H, J = 8.4 Hz, aryl)</td>
<td>70.14, 73.75, 110.74, 119.46, 121.28, 123.67, 127.39, 127.77, 128.37, 128.39, 128.98, 130.01, 130.06, 130.81, 137.33, 148.02, 154.33</td>
<td>293 (M⁺+1)</td>
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<td>4.29 (m, 4H, CH₂CH₂), 4.72 and 5.48 (both s, 4H, CH₂), 6.79 and 7.08 (both s, 2H, aryl), 7.25-7.35 (m, 2H, aryl), 7.55 and 7.78 (both d, 2H, J = 8.5 Hz, aryl)</td>
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<td>351 (M⁺+1)</td>
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<td>4.88 and 5.54 (both s, 4H, CH₂CH₂), 7.18 (m, 1H, pyridine), 7.26 (m, 1H, aryl), 7.37 (t, 1H, J = 7.6 Hz, aryl), 7.48-7.55 (m, 2H, aryl and pyridine), 7.79 (d, 1H, J = 8.0 Hz, aryl), 8.55 (d, 1H, J = 4.8 Hz, pyridine)</td>
<td>70.28, 72.87, 111.11, 119.54, 119.73, 121.30, 121.76, 123.78, 123.89, 127.11, 131.84, 132.23, 135.18, 136.80, 148.84, 151.48</td>
<td>294 (M⁺+1)</td>
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Compound 6 was identified by $^1$H NMR and LC-MS spectra only due to insufficient amount and stability.

**EXPERIMENTAL SECTION**

$^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury BB 400 MHz in CDCl$_3$ using HMDS as internal standard. LC-MS spectra were recorded on Alliance Waters 2695 instrument and Waters 3100 mass detector. 3-Chloromethylbenzo[4,5]imidazo[2,1-b]thiazole (1) was obtained from 2-mercaptobenzimidazole in the system CH$_2$COCH$_2$Cl / Me$_2$CO / H$_2$SO$_4$ according procedure 16. 2-Bromo-3-hydroxymethylpyrididine was prepared from corresponding aldehyde in the presence of NaBH$_4$ in ethanol. Cs$_2$CO$_3$, Pd(OAc)$_2$, Xantphos and 18-crown-6 (Acros and Aldrich) were used without additional purification.

**Typical procedure for the preparation of substituted 3-[2-bromophenyl(or pyridyl)methoxymethyl]benzo[4,5]imidazo[2,1-b]thiazoles 2-4.** Solid KOH (0.15 g, 2.7 mmol) was added to solution of 3-chloromethylbenzo[4,5]imidazo[2,1-b]thiazole (1) (0.20 g, 0.9 mmol), 2-bromobenzyl alcohols or 2-bromo-3-hydroxymethylpyridine (0.9 mmol), 18-crown-6 (0.024 g, 0.09 mmol) in dry toluene (30 ml) and the reaction mixture was refluxed for 2h. Then reaction mixture was filtered and solvent was removed under reduced pressure and crude residue was chromatographed on silica using ethyl acetate as eluent. See Table 1.

**Typical procedure for the preparation of five- and six-cyclic heterocyclic compounds 5-7.** Mixture of 3-[2-bromophenyl(or pyridyl)methoxymethyl]benzo[4,5]imidazo[2,1-b]thiazoles (1.2 mmol), Pd(OAc)$_2$ (0.03 g, 0.12 mmol), Xantphos (0.14 g, 0.24 mmol), anhydrous Cs$_2$CO$_3$ (0.78 g, 2.4 mmol), Ag$_2$CO$_3$ (0.17 g, 0.6 mmol) in dry toluene (5 ml) was heated at 135°C for 23 h in glass reactor under argon. Reaction mixture was diluted with ethyl acetate (30 ml), filtered and solvent was removed under reduced pressure and crude residue was chromatographed on silica using ethyl acetate : hexane in different mixtures as eluent. See Table 1.

**X-Ray crystallographic study of compound 5.** Diffraction data were collected at –90°C on a Bruker-Nonius KappaCCD diffractometer using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). The crystal structure of 5 was solved by direct methods 17 and refined by full-matrix least squares 18. All nonhydrogen atoms were refined in anisotropic approximation, all H-atoms were located from difference Fourier map and refined by riding model. Crystal data for 5: monoclinic; $a = 7.4743(1)$, $b = 7.1274(2)$, $c = 24.5610(6)$ Å, $\beta = 94.3471(9)^\circ$; $V = 1304.66(5)$ Å$^3$, $Z = 4$, $\mu = 0.247$ mm$^{-1}$; space group is $P 2_1/c$. A total of 3261 reflection intensities were collected up to 20$_{\text{max}} = 57^\circ$; for structure refinement 2457 independent reflections with $I > 3\sigma(I)$ were used. The final R-factor is 0.068. For further details, see crystallographic data for 5 deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 850017. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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