Supporting Information

Aminocarbonylation of 4-Iodo-1H-imidazoles with an Amino Acid Amide Nucleophile: Synthesis of Constrained H-Phe-Phe-NH₂ Analogues

Anna Skogh, Rebecca Fransson, Christian Sköld, Mats Larhed and Anja Sandström*

Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Center, Uppsala University, P. O. Box 574, SE-751 23 Uppsala, Sweden

*anja.sandstrom@orgfarm.uu.se

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1 General information

Compounds 1b, 4a-b and 4e-f are known and spectral data were in agreement with the proposed structures and matched those reported in the literature.

In order to screen different reaction conditions for the Pd-catalyzed C-5 arylation of 1-bensyl-1H-imidazole (Sm) a 2^4-1 fractional factorial design was used to systematically change temperature, reaction time, Pd-catalyst loading, and amount of aryl bromide (ArBr). The ratio of product (4b), 2,5-diarylated byproduct (4g), and remaining starting material in the crude reaction mixture were determined by ¹H NMR analysis and are reported in Table S1.

Table S1. Screening reaction conditions for C5 arylation of 1-bensyl-1H-imidazole with an aryl bromide.

<table>
<thead>
<tr>
<th>Exp no.</th>
<th>Time (min)</th>
<th>Temp. (ºC)</th>
<th>[Pd] (mol%)</th>
<th>ArBr (equiv.)</th>
<th>3b (%)^a</th>
<th>Sm (%)^a</th>
<th>3g (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>110</td>
<td>2</td>
<td>1</td>
<td>20</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>105</td>
<td>110</td>
<td>2</td>
<td>5</td>
<td>33</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>140</td>
<td>2</td>
<td>5</td>
<td>75</td>
<td>16</td>
<td>9</td>
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<tr>
<td>4</td>
<td>105</td>
<td>140</td>
<td>2</td>
<td>1</td>
<td>66</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>110</td>
<td>10</td>
<td>5</td>
<td>22</td>
<td>78</td>
<td>0</td>
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<tr>
<td>6</td>
<td>105</td>
<td>110</td>
<td>10</td>
<td>1</td>
<td>26</td>
<td>74</td>
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</tr>
<tr>
<td>7</td>
<td>45</td>
<td>140</td>
<td>10</td>
<td>1</td>
<td>20</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>105</td>
<td>140</td>
<td>10</td>
<td>5</td>
<td>68</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>75</td>
<td>125</td>
<td>6</td>
<td>3</td>
<td>71^a</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>125</td>
<td>6</td>
<td>3</td>
<td>71^a</td>
<td>22</td>
<td>7</td>
</tr>
</tbody>
</table>

Constant in all experiments: 1-Bensyl-1H-imidazole (1 mmol, 1 equiv), PivOH (0.3 equiv), K₂CO₃ (3 equiv), DMF (4.0 ml). The values are determined by ¹H NMR analysis. The reactions 9 and 10 were run with the same conditions to assess the experimental error.

Experiment 8, where all reaction parameters were maximized, resulted in full conversion of the starting material although with a high formation of byproduct (4g). Experiments 3, 9, and 10 gave highest product yields in combination with acceptable levels of byproduct formation. Hence, from this screening series we were satisfied with the experimental settings from
experiment 3 providing a low catalyst loading (2 mol%) and 5 equiv of the arylbromide. The compounds used in the $2^{4-1}$ fractional factorial design were synthesized in a Smith single mode reactor and to be able to repeat the $^1$H NMR ratios in Table 1 on an Initiator single mode reactor the reaction was run at 160 °C for 1h. These settings were chosen for the synthesis of the 5-aryl-1-benzyl-1H-imidazoles 4a–f without further optimization of the reaction.

Measurements of the volume of CO that was released from Mo(CO)$_6$ is shown in Figure S2. Chamber A was loaded with 0.2 mmol Mo(CO)$_6$. The two chambers were capped with a gas tight cap. Thereafter, 1,4-dioxane (3+3 mL), was added to both chambers by a syringe. Next, DBU (0.6 mmol) was added to chamber A by syringe and the two-chamber system was heated in a heating-block at 120 °C for 15-900 min under vigorous stirring. The expansion was measured with a gas tight syringe. The dead volume of the vial is 16 mL for reactions using 6 mL solvents. The maximum expansion, measured after 60 min, was approximately 20 mL. The pressure in these reactions, given from the data in Figure S1 is 2.25 bar.

![Figure S1. Volume of CO release using Mo(CO)$_6$ and DBU in 1,4-Dioxane at 120 °C.](image-url)
2 References

(2) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Marchetti, C.; Rossi, R. *Tetrahedron* **2008**, *64*, 6060.
3 NMR spectra, LC-MS and chiral HPLC chromatograms

Compound 1b

\[
\text{C}_{10}\text{H}_{6}\text{N}_{2}
\]

MWt: 284.1
Compound 3a

$C_{16}H_{16}N_2O_4S$

MW: 365.4
Compound 3a

![Chemical structure of Compound 3a with molecular weight 365.4](image)

![Graph showing chromatographic analysis](image)
Compound 3a

\[
\text{C}_{15}\text{H}_{19}\text{N}_{5}\text{O}_{4}\text{S}
\]

MW: 385.4

\[
\begin{align*}
\text{Minutes} & \quad 0.0 & \quad 5.0 & \quad 10.0 & \quad 15.0 & \quad 20.0 & \quad 23.0 \\
\% \text{ Mobile Phase} & \quad 0.0 & \quad 5.0 & \quad 10.0 & \quad 15.0 & \quad 20.0 & \quad 23.0 \\
\text{PV1} & \quad -5.0 & \quad 0.0 & \quad 5.0 & \quad 10.0 & \quad 15.0 & \quad 20.0 & \quad 23.0
\end{align*}
\]
Compound 3b

C_{20}H_{18}N_{4}O_{2}
MW: 348.4
Compound 3b

\[
\text{C}_2\text{H}_2\text{N}_2\text{O}_2
\]

MW: 348.4
Compound 3b

\[
\begin{align*}
\text{C}_{20}\text{H}_{21}\text{N}_{4}\text{O}_{2} \\
\text{MW: 348.4}
\end{align*}
\]
Compound 3b (corresponding D-form)

C_{20}H_{20}N_{2}O_{2}
MW: 348.4
Compound 4a

C_{10}H_{14}N_{2}
MW: 234.3
Compound 4b

C$_{17}$H$_{16}$N$_2$
MW: 248.3
Compound 4c

C_{17}H_{16}N_2
MW: 248.3
Compound 4c

![Chemical Structure](image)

C$_{17}$H$_{16}$N$_{2}$

MW: 248.3
Compound 4e

C_{17}H_{13}F_{3}N_{2}
MW: 302.2
Compound 4f

C<sub>17</sub>H<sub>12</sub>N<sub>2</sub>O
MW: 264.3
Compound 5a

C_{16}H_{12}N_{2}
MW: 360.2
Compound 5a

![Chemical Structure](image)

$C_{16}H_{15}N_2$

MW: 360.2

![Graph](image)
Compound 5b

C_{17}H_{18}N_{2}
MW: 374.2
Compound 5b

\[ \text{C}_{17}\text{H}_{16}\text{JN}_{2} \]

MW: 374.2
Compound 5c

C_{10}H_{18}N_{3}
MW: 374.2
Compound 5c

C_{37}H_{19}IN_{2}
MW: 374.2
Compound 5e

C_{17}H_{12}F_{3}N_{2}
MW: 428.2
Compound 5e

\[
\text{C}_{11}\text{H}_{12}\text{F}_3\text{IN}_2
\]

MW: 429.2
Compound 5f

C$_{13}$H$_{14}$N$_2$O
MW: 390.2
Compound 5f

C_{17}H_{16}N_{2}O
MW: 390.2
Compound 6a

C_{26}H_{24}N_4O_2
MW: 424.5
Compound 6a

C$_{26}$H$_{24}$N$_4$O$_2$

MW: 424.5
Compound 6a

C$_{26}$H$_{24}$N$_4$O$_2$
MW: 424.5
Compound 6b

C$_{27}$H$_{28}$N$_4$O$_2$
MW: 438.5
Compound 6b
Compound 6b

C_{21}H_{36}N_2O_2
MW: 438.5
Compound 6c

C_{27}H_{26}N_{4}O_{2}
MW: 438.5
Compound 6c

C_{27}H_{28}N_{4}O_{2}
MW: 438.5
Compound 6c

C_{27}H_{26}N_{4}O_{2}
MW: 438.5
Compound 6e

C_{27}H_{33}F_{3}N_{4}O_{2}
MW: 492.5

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Compound 6e

**Chemical Structure**

![Chemical Structure of Compound 6e](image)

**Molecular Formula**

C$_2$H$_{23}$F$_3$N$_4$O$_2$

**Molecular Weight**

492.5

**Additional Information**

- MS, 1.8 min, m/z 425.27
Compound 6e
Compound 6f

C_{27}H_{20}N_{4}O_{3}
MW: 454.5
Compound 6f
Compound 6f

\[ \text{C}_{27}\text{H}_{26}\text{N}_{4}\text{O}_{3} \]

MW: 454.5
Compound 6f (corresponding D-form)

C$_2$H$_{28}$N$_4$O$_3$
MW: 454.5
Compound 7a

C$_{12}$H$_{14}$N$_2$O$_2$
MW 258.3
Compound 7a

![Chemical Structure]

C_{14}H_{16}N_{4}O_{2}

MW: 258.3
Compound I

C_{19}H_{18}N_{2}O_{2}
MW: 334.4
Compound I