Copper or Palladium Catalyzed Amidation and Cyclization Route to the Synthesis of Pyrimido[4,5-b]carbazoles

Arepalli Sateesh Kumar and Rajagopal Nagarajan*

School of chemistry, University of Hyderabad, Hyderabad - 500046.

rnsc@uohyd.ernet.in

SUPPORTING INFORMATION

Table of Contents

<table>
<thead>
<tr>
<th>Table of Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Information</td>
<td>S2</td>
</tr>
<tr>
<td>Materials</td>
<td>S2</td>
</tr>
<tr>
<td>General Procedures</td>
<td>S3-S5</td>
</tr>
<tr>
<td>Spectra, LC-MS and Elemental Analysis</td>
<td>S6-S55</td>
</tr>
</tbody>
</table>
**General Information:**

The $^1$H NMR and $^{13}$C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for $^1$H NMR and relative to the central CDCl$_3$ resonance ($\delta = 77.0$) for $^{13}$C NMR. *In the $^{13}$C NMR spectra, the nature of the carbons (C, CH, CH$_2$ or CH$_3$) was determined by recording the DEPT-135 experiment, and is given in parentheses.* The coupling constants $J$ are given in Hz. IR spectra were recorded on JASCO FT/IR-5300. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010 A mass spectrometer. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used. The procedures does not require inert atmosphere. All the products obtained were purified by column chromatography using silica gel (100-200 mesh). Hexane was used as a co-eluent. Melting points were measured in open capillary tubes and are uncorrected.

**Materials:**

All the solvents and commercially available reagents were used as received.
General Procedure A for the Copper-Catalyzed Amidation of 2-halo-9H-carbazole-3-carbaldehydes

An oven-dried Ace-pressure tube with a Teflon stir bar was charged with amide (1.2 equiv, 0.60 mmol), CuI (10 mol %, 0.05 mmol), base (2.0 equiv, 1 mmol), and approximately 200 mg of activated 4Å molecular sieves, 2-halo-9H-carbazole-3-carbaldehydes (1.0 equiv, 0.50 mmol), trans-N,N-dimethylcyclohexane-1,2-diamine (L3) (20 mol %, 0.1 mmol), and 1,4-dioxane (5 mL) were each added. The pressure tube was then capped with a Teflon screw cap placed in a preheated oil bath at 110 °C. The reaction was heated with stirring for according time mentioned in Table 2 and then cooled to room temperature. The reaction mixture was partitioned between EtOAc and water and the organic layer was separated. The aqueous layer was extracted with EtOAc and the organic layers were combined, dried over sodium sulphate, filtered, and concentrated in vacuo to remove solvent. The product was purified by column chromatography on after silica gel with EtOAc and hexanes afforded N-(9-substituted-3-formyl-9H-carbazol-2-yl)amides 3a-f.

General Procedure B for the Pd-catalyzed amidation of 2-halo-9H-carbazole-3-carbaldehydes

An oven dried Ace Pressure tube with Teflon stir bar was charged with Pd2(dba)3 (0.50 mol %, 1.0 mol % Pd), BINAP (0.25 mol %), amide (1.2 equiv) and Cs2CO3 (3.0 equiv), 2-halo-3-carbonylindoles (1.0 equiv) and if X = Br, toluene (2.0 mL); X = Cl, t-BuOH (2.0 mL) and then capped with a Teflon screw cap and the mixture was heated to 110 °C with stirring according to mentioned time in Tables 3. At this point, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and the resulting solution was filtered through celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on after silica gel (eluting with hexanes/ethyl acetate) to gave the corresponding coupled products N-(9-substituted-3-formyl-9H-carbazol-2-yl)amides 3a-f.
General procedure for the two-step synthesis of pyrimido[4,5-b]carbazole (Method A):

In the step 1, follow the copper- or palladium-catalyzed amidation procedures to obtain pure amide derivatives such as \(N\)-(9-substituted-3-formyl-9H-carbazol-2-yl)amides 3a-f as shown in Tables 2 & 3 respectively and then in the step 2, an oven dried Ace Pressure tube with Teflon stir bar was charged with \(N\)-(9-substituted-3-formyl-9H-carbazol-2-yl)amides 3a-f (1.0 equiv) and HCOONH₄ (6.0 equiv) in \(t\)-BuOH (6 mL). The pressure tube was then sealed with a Teflon screw-cap and the reaction was placed in a preheated oil bath at 110 °C. The reaction mixture was stirred for according to mentioned time in Table 4 and then removed from the oil bath and allowed to cool to room temperature. The reaction mixture was then diluted with ethyl acetate. The resultant reaction mixture was extracted with EtOAc (20 mL), washed with water (100 mL) and dried over anhydrous Na₂SO₄. The solvent was removed \textit{in vacuo} to obtain the pure product (4a-f). Hexane was added and removed twice more before the product was dried \textit{in vacuo}.

General procedure for the one-pot, single step (sequential amidation and cyclization) synthesis of pyrimido[4,5-b]carbazole (Method B):

An oven dried Ace Pressure tube with Teflon stir bar was charged with Pd₂dba₃ (1.3 mg, 1.4 \(\mu\)mol, 1.0 mol % Pd), BINAP (0.18 mg, 2.9 \(\mu\)mol, 1.5 mol %), amide (86 mg, 0.07 mmol) and base [Cs₂CO₃ (195 mg) or K₃PO₄ (127 mg) or K₂CO₃ (83 mg) or \(t\)-BuOK (58 mg), 3-halo-2-formylindoles or 2-halo-3-carbonylindoles (0.150g ,5.9 \(\mu\)mol) and \(t\)-BuOH (2.0 mL) and then capped with a Teflon screw cap and the mixture was heated to 110 °C with stirring and the reaction was monitored by TLC.

(or)

An oven-dried Ace-pressure tube with a Teflon stir bar was charged with amide (1.2 equiv, 0.60 mmol), CuI (10 mol %, 0.05 mmol), base (2.0 equiv, 1 mmol), and approximately 200 mg of activated 4Å molecular sieves, 2-halo-9\(H\)-carbazole-3-carbaldehydes (1.0 equiv, 0.50 mmol), \textit{trans-}N,N-dimethylcyclohexane-1,2-diamine (L3) (20 mol %, 0.1 mmol), and 1,4-dioxane (5 mL) were each added. The pressure tube was then capped with a Teflon screw cap placed in a preheated oil bath at 110 °C. The reaction was heated with stirring for 24 h and
then cooled to room temperature. When the starting material was completely consumed, the reaction mixture was cooled to <80 °C and HCOONH₄ (6.0 equiv) in t-BuOH (2 mL) was added in one portion. The resulting mixture was heated back to 110 °C and the reaction mixture was stirred for according time mentioned in Table 4. When the reaction was complete, reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and the resulting solution was filtered through celite, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with hexanes/ethyl acetate) to gave the corresponding pyrimido[4,5-b]carbazole 4a-f products.
$^1$H NMR of N-(9-ethyl-3-formyl-6-methyl-9H-carbazol-2-yl)benzamide (3a)
$^{13}$C NMR of $N$-(9-ethyl-3-formyl-6-methyl-9\textit{H}-carbazol-2-yl)benzamide (3a)
DEPT of $N$-(9-ethyl-3-formyl-6-methyl-9$H$-carbazol-2-yl)benzamide (3a)
LCMS of \( N\)-(9-ethyl-3-formyl-6-methyl-9\textit{H}-carbazol-2-yl)benzamide (3a)
CHN Analysis of \( N-(9\text{-ethyl-3-formyl-6-methyl-9}H\text{-carbazol-2-yl})\text{benzamide} \) (3a)
$^1$H NMR of $N$-(9-ethyl-3-formyl-6-methyl-9$H$-carbazol-2-yl)nicotinamide (3b)
$^{13}$C NMR of $N$-(9-ethyl-3-formyl-6-methyl-9H-carbazol-2-yl)nicotinamide (3b)
LCMS of $N$-(9-ethyl-3-formyl-6-methyl-9$H$-carbazol-2-yl)nicotinamide (3b)
CHN Analysis of \( N-(9\text{-ethyl-3-formyl-6-methyl-9H-carbazol-2-yl})\text{nicotinamide (3b)} \)
$^1$H NMR of $N$-(9-ethyl-3-formyl-9$H$-carbazol-2-yl)nicotinamide (3c)
\(^{13}\)C NMR of \(N\)-(9-ethyl-3-formyl-9H-carbazol-2-yl)nicotinamide (3c)
LCMS of $N$-(9-ethyl-3-formyl-9H-carbazol-2-yl)nicotinamide (3c)
CHN Analysis of \( \text{N-}(9\text{-ethyl-3-formyl-9}\text{H-carbazol-2-yl})\text{nicotinamide (3c)} \)
$^1$H NMR $N$-(9-ethyl-3-formyl-9$H$-carbazol-2-yl)benzamide (3d)
$^{13}$C NMR of $N$-(9-ethyl-3-formyl-9$H$-carbazol-2-yl)benzamide (3d)
LCMS of \(N-(9\text{-ethyl-3-formyl-9H-carbazol-2-yl})\)benzamide (3d)
CHN Analysis of \( N-(9\text{-ethyl-3-formyl-9}\text{H-carbazol-2-yl})\text{benzamide (3d)} \)
$^1$H NMR of $N$-(9-butyl-3-formyl-9$H$-carbazol-2-yl)nicotinamide (3e)
$^{13}$C NMR of $N$-(9-butyl-3-formyl-9$H$-carbazol-2-yl)nicotinamide (3e)
LCMS of N-(9-butyl-3-formyl-9H-carbazol-2-yl)nicotinamide (3e)
CHN Analysis of $N$-(9-butyl-3-formyl-9H-carbazol-2-yl)nicotinamide (3e)

<table>
<thead>
<tr>
<th>Element Name</th>
<th>Element %</th>
<th>Ret. Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen</td>
<td>11.45</td>
<td>0.90</td>
</tr>
<tr>
<td>Carbon</td>
<td>74.21</td>
<td>1.48</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>5.78</td>
<td>4.77</td>
</tr>
</tbody>
</table>
$^1$H NMR of $N$-(9-butyl-3-formyl-9H-carbazol-2-yl)acetamide (3f)
$^{13}$C NMR of $N$-(9-butyl-3-formyl-9H-carbazol-2-yl)acetamide (3f)
LCMS of $N$-(9-butyl-3-formyl-9$H$-carbazol-2-yl)acetamide (3f)
CHN Analysis of N-(9-butyl-3-formyl-9H-carbazol-2-yl)acetamide (3f)
$^1$H NMR of 10-ethyl-2-phenyl-10H-pyrimido[4,5-b]carbazole (4a)
$^{13}$C NMR of 10-ethyl-2-phenyl-10$H$-pyrimido[4,5-$b$]carbazole (4a)
LCMS of 10-ethyl-2-phenyl-10H-pyrimido[4,5-b]carbazole (4a)
CHN Analysis of 10-ethyl-2-phenyl-10H-pyrimido[4,5-b]carbazole (4a)
$^1$H NMR of 10-Ethyl-2-(pyridin-3-yl)-10H-pyrimido[4,5-b]carbazole (4b)
$^{13}$C NMR of 10-Ethyl-2-(pyridin-3-yl)-10$H$-pyrimido[4,5-$b$]carbazole (4b)
LCMS of 10-Ethyl-2-(pyridin-3-yl)-10H-pyrimido[4,5-b]carbazole (4b)
CHN Analysis of 10-Ethyl-2-(pyridin-3-yl)-10H-pyrimido[4,5-b]carbazole (4b)
$^1$H NMR of 10-ethyl-7-methyl-2-phenyl-10$H$-pyrimido[4,5-\textit{b}]carbazole (4c)
$^{13}$C NMR of 10-ethyl-7-methyl-2-phenyl-10H-pyrimido[4,5-b]carbazole (4c)
DEPT of 10-ethyl-7-methyl-2-phenyl-10H-pyrimido[4,5-b]carbazole (4c)
LCMS of 10-ethyl-7-methyl-2-phenyl-10H-pyrimido[4,5-b]carbazole (4c)
CHN Analysis of 10-ethyl-7-methyl-2-phenyl-10H-pyrimido[4,5-b]carbazole (4c)
$^1$H NMR of 10-ethyl-7-methyl-2-(pyridin-3-yl)-10$H$-pyrimido[4,5-b]carbazole (4d)
$^{13}$C NMR of 10-ethyl-7-methyl-2-(pyridin-3-yl)-10$H$-pyrimido[4,5-$b$]carbazole (4d)
LCMS of 10-ethyl-7-methyl-2-(pyridin-3-yl)-10$H$-pyrimido[4,5-$b$]carbazole (4d)
CHN Analysis of 10-ethyl-7-methyl-2-(pyridin-3-yl)-10H-pyrimido[4,5-b]carbazole (4d)
$^1$H NMR of 10-butyl-2-(pyridin-3-yl)-10H-pyrimido[4,5-b]carbazole (4e)
$^{13}\text{C} \text{NMR of } 10\text{-butyl}-2\text{-}(\text{pyridin-3-yl})\text{-}10\text{H}\text{-pyrimido[4,5-b]carbazole (4e)}$
LCMS of 10-butyl-2-(pyridin-3-yl)-10H-pyrimido[4,5-b]carbazole (4e)
CHN Analysis of 10-butyl-2-(pyridin-3-yl)-10H-pyrimido[4,5-b]carbazole (4e)

<table>
<thead>
<tr>
<th>Element Name</th>
<th>Element %</th>
<th>Ret. Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen</td>
<td>15.81</td>
<td>0.76</td>
</tr>
<tr>
<td>Carbon</td>
<td>78.21</td>
<td>1.13</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>5.92</td>
<td>3.83</td>
</tr>
</tbody>
</table>
$^{1}$H NMR of 10-butyl-2-methyl-10$H$-pyrimido[4,5-$b$]carbazole (4f)
$^{13}$C NMR of 10-butyl-2-methyl-10$H$-pyrimido[4,5-$b$]carbazole (4f)
LCMS of 10-butyl-2-methyl-10H-pyrimido[4,5-b]carbazole (4f)
CHN Analysis of 10-butyl-2-methyl-10H-pyrimido[4,5-b]carbazole (4f)