Palladium-Mediated Heck Reaction to the Synthesis of 3-Substituted Indoles and Indolones

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Abstract: A simple and straightforward palladium-mediated ligand-free Heck coupling reaction for the synthesis of 3-substituted indoles and indolones framework has been achieved.

Key words: Heck reaction, indoles, indolones, Pd(OAc)₂

The palladium-catalyzed coupling of olefins with aryl or vinyl halides, known as the Heck reaction, is one of the most powerful methods to form a new carbon–carbon bond in modern chemistry. The Heck reaction provides a direct route to assemble important arylated and vinylated olefins, and its wide functional group tolerance on both reactants allows its convenient application in multistep synthesis. The indole ring is prevalent in a wide variety of natural and synthetic products, many of which are capable of binding to biological receptors with high affinity.1,2 Accordingly, indoles have been referred to as ‘privileged structure’ in pharmaceutical field. Their synthesis has been a focus for many years.3–9 On the other hand compounds containing the indol-2-one scaffold constitute an important pharmacophoric moiety, which exhibits important biological activities such as antitumor activity,10,11 phosphodiesterase inhibitor activity,12 and tyrosine kinase inhibitor activity.13,14 These examples illustrate the recent interest towards the scaffolds containing indole-2-one.

We were interested in the synthesis of polynuclear coumarin and quinolone derivatives due to their widespread applicability.15–19 Recently, we have also succeeded to synthesize pyran[3,2-ε]indolone and pyrrolo[3,2-f]quinolone derivatives through Pd(0)-mediated cross coupling followed by Cu(I)-catalyzed hetero annulation.20 In this report, we present a simple ligand-free Heck approach towards the synthesis of 3-substituted indoles and indolone frame work from simple coumarin, quinolone, and naphthyl amines.

The requisite precursors for our present synthesis of 3-substituted indole framework were synthesized in 70–90% yields by simple bromination of N-allyl derivatives or N-methyl-N-allyl derivatives or N,N-diallyl derivatives of the corresponding amines with N-bromosuccinimide (1 equiv) in acetonitrile at room temperature for about 20 to 60 minutes as outlined in Scheme 1.

Scheme 1  Reagents and conditions: (i) NBS, MeCN, 25 °C, 24–60 min.

All attempts of substitution on nitrogen atom of the corresponding amines after bromination failed. We therefore conducted bromination after the substitution reaction. Under the aforesaid condition bromination occurred only at the o-position with respect to the nitrogen atom of the amines without affecting the allylic position to give exclusively one bromo product 2a–e, 4b, and 5b. When the intramolecular Heck reaction was carried out with 2a in the presence of 10 mol% Pd(OAc)₂ as catalyst, KOAc (1.5 equiv) as a base, and TBAB as promoter in DMF at 100 °C for 24 minutes, the cyclized derivative 3a was obtained in 95% yield (Table 1; for the structure of 3a, see Table 2). Carrying out several experiments on substrate 2a achieved the optimized condition. Various catalytic systems were investigated: different sources of palladium, including Pd(PPh₃)₄Cl₂, Pd(PPh₃)₂Cl₂, PdCl₂, Pd(OAc)₂ with KOAc in DMF; however, only Pd(OAc)₂ provided the desired cyclized product 3a in 95% yield. We then conducted the same reaction at various temperatures and it was observed that at higher temperatures several unidentified products were obtained along with a lower amount of the
desired cyclized product. Among several aprotic polar solvents examined, DMF gave the highest yield of the product, while DMSO and MeCN were found to give lower yields of the product. Among the various bases used KOAc was found to be more effective than others. The results are summarized in Table 1.

Substrate 2b–e and 4b reacted under the conditions described in entry 1, Table 1, to afford the desired cyclized products (Table 2).

Usually a ligand is necessary for this type of cyclization, but in our case we obtained the desired cyclized products without the use of any ligands. However, substrate 5b under the same set of conditions gave only the debrominated product 5a (Scheme 2).

![Scheme 2](image)

Table 1: Cyclization of 2a to 3a under Heck Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst(^a)</th>
<th>Base(^b)</th>
<th>Solvent</th>
<th>Yield of 3a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)_2</td>
<td>KOAc</td>
<td>DMF</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh_3)_2Cl</td>
<td>KOAc</td>
<td>DMF</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh_3)_4</td>
<td>KOAc</td>
<td>DMF</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>PdCl_2</td>
<td>KOAc</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)_2</td>
<td>Cs_2CO_3</td>
<td>DMF</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)_2</td>
<td>Et_3N</td>
<td>DMF</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)_2</td>
<td>KOAc</td>
<td>DMSO</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)_2</td>
<td>KOAc</td>
<td>MeCN</td>
<td>10</td>
</tr>
</tbody>
</table>

*TBAB was used as promoter. All the reactions were performed at 100 °C for 24 min.
\(^b\) Amount of catalyst used: 10 mol%.
\(^c\) Amount of base used: 1.5 equiv.

Table 2: Results of Heck Cyclization of the Bromo Derivatives 2a–e and 4b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor</th>
<th>Time (min)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>24</td>
<td>3a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>18</td>
<td>3b</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>48</td>
<td>3c</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>18</td>
<td>3d</td>
<td>75</td>
</tr>
</tbody>
</table>
On the other hand, the requisite precursors 8a,b for 3-substituted indolones were synthesized by the reaction of 7a,b with cinnamoyl chloride in anhydrous CH$_2$Cl$_2$ in the presence of triethylamine as a base and DMAP as a catalyst at 25 °C for 3–4 hours in 85–90% yields. The substrates 7a,b in turn were prepared by the bromination of the corresponding precursors 6a,b with N-bromosuccinimide in acetonitrile at 25 °C for 15–30 minutes (Scheme 3).

When the intramolecular Heck reaction was carried out with 8a in the presence of 10 mol% Pd(OAc)$_2$ as a catalyst and KOAc (1.5 equiv) as a base and tetrabutylammonium bromide as a promoter in DMF at 80 °C for 30 minutes, the cyclized derivative 9a was obtained in 75% yield (Table 3).

The optimized conditions for the Heck cyclization was achieved through a series of experiments where sequential changes were made to the catalyst, temperature, base, and solvent used. The effect was more or less the same as for Heck cyclization to prepare 3-substituted indole framework (presented in Table 1). Substrate 8b under a similar

![Scheme 3: Reactions and conditions](image)

**Table 3** Heck Cyclization of the Amides 8a and 8b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor</th>
<th>Time (min)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>30</td>
<td>9a</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>8b</td>
<td>36</td>
<td>9b</td>
<td>80</td>
</tr>
</tbody>
</table>

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set of conditions gave the desired cyclized product 9b in 80% yield.

Regioselective syntheses of pyrano [3,2-e]indolo-7(3H)-ones and pyrrolo[3,2-f]quinolin-7(6H)-ones have earlier been reported through a long route involving successive tosylation, methylation, detosylation, prop-2-ynylation, and MCPBA treatment followed by hydrolysis of the resulting ester. The protocol is only applicable to tertiary amine substrates. The present method involves fewer steps and also applicable to secondary amine system.

In conclusion, we have developed a ligand free Heck reaction for the synthesis of hitherto unreported 3-substituted indole and indolone moieties found in bioactive compounds. This protocol is equally effective towards the substituted or unsubstituted amine system and it is also applicable to substituted amide system. In the case of N,N-diallyl system, one double bond take parts in the reaction and other remain intact under Heck conditions.

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded (cm⁻¹) using neat liquids and solid samples were recorded in KBr disks. 1H NMR (400 MHz) spectra were recorded in CDCl₃ (chemical shift in δ) with TMS as internal standard. Silica gel [60–120, 230–400 mesh], Spectrochem, India] was used for chromatographic separation. Silica gel G [E. Merck (India)] was used for TLC. Petroleum ether (PE) refers to the fraction boiling in the range 60–80 °C.

6-(Allylamino)-5-bromo-2H-chromen-2-one (2a); Typical Procedure
A mixture of 6-(allylamino)-2H-chromen-2-one (1a; 0.5 g, 2.48 mmol), N-bromosuccinimide (0.44 g, 2.48 mmol) in MeCN (25 mL) was stirred at r.t. for 30 min. After completion of the reaction, the solvent was removed and the residue was extracted with CH₂Cl₂ (3 × 15 mL). The combined CH₂Cl₂ layers were washed with H₂O (3 × 10 mL) and dried (Na₂SO₄). The solvent was removed and the residual mass was purified by column chromatography over silica gel using PE–Et₂OAc (9:1) as eluent to afford the brominated product 2a; yield: 557 mg (80%); yellow solid; mp 120–122 °C.
IR (KBr): 3380, 1600 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 3.87 (d, J = 5.6 Hz, 2 H), 4.56 (br s, 1 H), 5.19–5.29 (m, 2 H), 5.84–5.93 (m, 2 H), 6.73 (d, J = 9.8 Hz, 1 H), 7.01 (d, J = 9.4 Hz, 1 H), 7.22 (d, J = 8.9 Hz, 1 H), 8.03 (d, J = 9.4 Hz, 1 H).
MS: m/z = 292 (M⁺), 294 (M⁺ + 2).
Anal. Calcd for C₁₃H₁₁BrNO₂: C, 55.60; H, 3.76; N, 5.33. Found: C, 55.65; H, 3.77; N, 5.10.

6-(Diallylamino)-5-bromo-2H-chromen-2-one (2b); Typical Procedure
A mixture of 6-(diallylamino)-2H-chromen-2-one (1b; 0.357 mmol), TBAB (172 mg, 0.53 mmol), Pd(OAc)₂ (8.0 mg, 3.5 × 10⁻⁴ mmol) in anhyd DMF (5 mL) was heated at 100 °C for 0.4 h. The mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined CH₂Cl₂ extracts were washed with H₂O (3 × 7 mL) and dried (Na₂SO₄). The solvent was removed and the residual mass was purified by column chromatography over silica gel using PE–Et₂OAc (4:1) as eluent to afford 3a; yield: 67.5 mg (95%); yellow solid; mp 170–172 °C.
IR (KBr): 2885, 1600 cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 3.74 (d, J = 5.8 Hz, 4 H), 5.11–5.23 (m, 4 H), 5.78–5.88 (m, 2 H), 6.91 (d, J = 7.9 Hz, 1 H), 7.50–7.58 (m, 2 H), 7.66 (d, J = 7.9 Hz, 1 H), 8.18 (d, J = 8.2 Hz, 1 H), 8.29 (d, J = 8.1 Hz, 1 H).
MS: m/z = 301 (M⁺), 303 (M⁺ + 2).
Anal. Calcd for C₁₅H₁₄BrNO₂: C, 56.59; H, 5.34; N, 4.63. Found: C, 56.71; H, 5.50; N, 4.73.

N,N-Diallyl-1-bromonaphthalen-2-amine (4b)
Yield: 85%; yellow liquid.
IR (KBr): 2885, 1600 cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 3.74 (d, J = 5.8 Hz, 4 H), 5.11–5.23 (m, 4 H), 5.78–5.88 (m, 2 H), 6.91 (d, J = 7.9 Hz, 1 H), 7.50–7.58 (m, 2 H), 7.66 (d, J = 7.9 Hz, 1 H), 8.18 (d, J = 8.2 Hz, 1 H), 8.29 (d, J = 8.1 Hz, 1 H).
MS: m/z = 301 (M⁺), 303 (M⁺ + 2).
Anal. Calcd for C₁₅H₁₄BrN: C, 56.50; H, 4.63; N, 4.73.

Heck Reaction of Substrates 2a–e and 4a; 1-Methylpyrano[3,2-e]indolo-7(3H)-one (3a); Typical Procedure
A mixture of 2a (100 mg, 0.357 mmol), TBAB (172 mg, 0.53 mmol), KOAc (52 mg, 0.53 mmol), Pd(OAc)₂ (8.0 mg, 3.5 × 10⁻⁴ mmol) in anhyd DMF (5 mL) was heated at 100 °C for 0.4 h. The mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined CH₂Cl₂ extracts were washed with H₂O (3 × 7 mL) and dried (Na₂SO₄). The solvent was removed and the residual mass was purified by column chromatography over silica gel using PE–Et₂OAc (4:1) as eluent to afford 3a; yield: 67.5 mg (95%); yellow solid; mp 170–172 °C.
IR (KBr): 2885, 1720 cm⁻¹.
1H NMR (400 MHz, DMSO-d₆): δ = 2.49 (s, 3 H), 6.43 (d, J = 9.6 Hz, 1 H), 7.11 (d, J = 8.7 Hz, 1 H), 7.35 (s, 1 H), 7.60 (d, J = 8.7 Hz, 1 H), 8.49 (d, J = 9.6 Hz, 1 H), 11.28 (s, 1 H).
MS: m/z = 199 (M⁺).

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Anal. Calcd for C_{15}H_{13}NO_{2}: C, 75.30; H, 5.48; N, 5.85. Found: C, 76.30; H, 6.53; N, 11.19.

1,6-Dimethyl-3H-pyrrolo[3,2-f]quinolin-7(6H)-one (3d)
Yield: 85%; yellow solid; mp 190–192 °C.

IR (KBr): 1660, 1590 cm–1.

Anal. Calcd for C_{19}H_{13}NO_{3}: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.51; H, 4.58; N, 4.70.

1,6-Dimethyl-3H-pyrrolo[3,2-f]quinolin-7(6H)-one (3e)
Yield: 85%; viscous liquid.

IR (KBr): 3330, 1650 cm–1.

Anal. Calcd for C_{19}H_{14}BrNO_{3}: C, 59.39; H, 3.67; N, 3.65. Found: C, 59.62; H, 3.82; N, 3.75.

Heck Reaction of Amides; 1-Benzylidene-3-methylpyrano[3,2-e]indole-2,7(3H)-dione (9a)
Typical Procedure
A mixture of 8a (100 mg, 0.260 mmol), TBAB (125 mg, 0.39 mmol), KOAoc (38 mg, 0.39 mmol), Pd(OAc)_{2} (8.7 mg, 3 × 10^{-4} mmol) in anhyd DMF (5 mL) was heated at 80 °C for 0.5 h. After completion of the reaction, the mixture was washed with H_{2}O (3 × 15 mL) and dried (Na_{2}SO_{4}). The solvent was removed and the residual mass was purified by column chromatography over silica gel using PE–EtOAc (4:1) as eluant to afford 9a; yield: 640 mg (85%); yellow solid; mp 190–192 °C.

IR (KBr): 1650 cm–1.

1H NMR (400 MHz, CDCl_{3}); δ = 3.29 (s, 3 H), 6.02 (d, J = 15.4 Hz, 1 H), 6.53 (d, J = 9.8 Hz, 1 H), 7.22–7.27 (m, 5 H), 7.35 (d, J = 8.7 Hz, 1 H), 7.45 (d, J = 8.7 Hz, 1 H), 7.66 (d, J = 15.4 Hz, 1 H), 8.09 (d, J = 9.8 Hz, 1 H).

MS: m/z = 383 (M^{+}), 385 (M^{+} + 2).

Anal. Calcd for C_{14}H_{12}BrN_{2}O; C, 59.39; H, 3.67; N, 3.65. Found: C, 59.62; H, 3.82; N, 3.75.

1-Benzylidene-6-ethyl-3-methyl-1H-pyrrolo[3,2-f]quinolin-7(6H)-one (9b)

Yield: 90%; yellow solid; mp 174–176 °C.

IR (KBr): 1658, 1605 cm–1.

1H NMR (400 MHz, CDCl_{3}); δ = 1.37 (t, J = 7.0 Hz, 3 H), 3.33 (s, 3 H), 4.30 (q, J = 7.0 Hz, 2 H), 6.09 (d, J = 15.5 Hz, 1 H), 6.83 (d, J = 9.8 Hz, 1 H), 7.26–7.27 (m, 5 H), 7.40 (d, J = 9.1 Hz, 1 H), 7.47 (d, J = 9.1 Hz, 1 H), 7.72 (d, J = 15.5 Hz, 1 H), 8.19 (d, J = 9.8 Hz, 1 H).

MS: m/z = 410 (M^{+}), 412 (M^{+} + 2).

Anal. Calcd for C_{17}H_{15}BrN_{2}O; C, 61.33; H, 4.66; N, 8.19. Found: C, 61.55; H, 4.81; N, 6.93.
Anal. Calcd for C_{21}H_{18}N_{2}O_{2}: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.51; H, 5.60; N, 8.56.

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References