STEREOSELECTIVE SYNTHESIS OF 1-INDANYLIDENE SUBSTITUTED HETEROAROMATIC DERIVATIVES VIA Pd-CATALYZED TANDEM INSERTION AND CROSS COUPLING REACTIONS

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Abstract - Treatment of 4-(o-iodophenyl)-1-butyne with a variety of heteroarylzinc chlorides in the presence of a catalytic amount of Pd(PPh₃)₄ gave (Z)-1-indanylidene substituted heteroaromatics in moderate to good yields with high Z-selectivities.

The palladium-catalyzed reactions of either alkynes and alkenes with organic halides or organozinc chlorides with organic halides have been extensively studied to provide a good approach to form carbon-carbon bond.⁴ Although particular attention has been paid to the former type reaction, also known as "Heck reaction", the number of papers reporting the potential utility of the Pd(II)-intermediate, obtained from the insertion of alkyne group, are still very small.⁵-¹²

Recently we have found that the Pd(II)-intermediate obtained in situ from intramolecular arylation of alkynes can be further cross coupled with phenylzinc chloride and gave stereo-defined exocyclic indan and tetralin derivatives.¹³ The undesired coupling products were obtained only in 2-25% yields.

We now report that a variety of heteroarylzinc chlorides can indeed be readily cross coupled with the Pd(II)-intermediate, obtained rapidly from 4-(o-iodophenyl)-1-butyne(1) and a catalytic amount of Pd(PPh₃)₄, to give (Z)-1-indanylidene substituted heteroaromatics in moderate to good yields. As representative heteroaromatics 2- and 3-pyridyl, 2-furyl, 2-thienyl, 2-N-methylpyrrolyl, and 2-benzothiazolyl were chosen. As indicated by the structures of the products(2) to 7 as well as by the results summarized in the Table I, syntheses of the stereo-defined 1-indanylidene substituted systems can now be readily achieved by the Pd-catalyzed intramolecular insertion and cross coupling processes. Their stereochemistry was again determined by their ¹H-nmr as well as 2D NOESY.
Table I. The Reaction of 1 with Heteroarylzinc Chlorides in the Presence of Pd(0) Catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Heteroarylzinc Chloride $^a$</th>
<th>Product</th>
<th>Yield $^b$ (%)</th>
<th>Byproduct (%) $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>N</strong></td>
<td>2</td>
<td>66</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td><strong>N</strong></td>
<td>3</td>
<td>53</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td><strong>F</strong></td>
<td>4</td>
<td>58</td>
<td>8 (28)</td>
</tr>
<tr>
<td>4</td>
<td><strong>F</strong></td>
<td>5</td>
<td>74</td>
<td>9 (6)</td>
</tr>
<tr>
<td>5</td>
<td><strong>N</strong></td>
<td>6</td>
<td>52</td>
<td>10 (33)</td>
</tr>
<tr>
<td>6</td>
<td><strong>N</strong></td>
<td>7</td>
<td>70</td>
<td>11 (21)</td>
</tr>
</tbody>
</table>

$^a$ Heteroarylzinc chlorides were prepared by treating the corresponding organolithium with one equivalent of dry ZnCl$_2$ in THF.

$^b$ Isolated yields of pure products.

spectral analyses. While the yield of uncyclized products obtained from either 2-pyridyl- or 3-pyridylzinc chloride is only trace amount, the isolated yields of uncyclized products (8-11) are between 6-33%.

On the basis of the current study, it is clear that this methodology could be extended to the preparation of other valuable derivatives of stereo-defined and carbo-substituted heteroaromatics. In fact, until the present time, the preparation of (Z)-1-indanylidene substituted heteroaromatics has rarely been reported. 14
EXPERIMENTAL SECTION

Melting points are uncorrected. Precoated silica gel 60F-254 on aluminum plates made by EM Chemical Company were used for thin layer chromatography. Purification by column chromatography was carried out with EM Reagents silica gel 60 (70-230 mesh ASTM). Glc analyses were performed on a 3.2 m x 3.1 mm column packed with SE-30 (5% on chromosorb W). The purity of all title compounds was judged to be >95% by gc, 'H-nmr, as well as 13C-nmr spectra analysis. Zinc chloride was dried before use at 100°C at 1 mmHg for 3 h. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use.

(Z)-2-(1-Indanylidenemethyl)pyridine 2. A Representative Procedure for Pd-
Catalyzed Stereoselective Synthesis of 1-Indanylidene Substituted Heteroaromatics via Insertion and Cross Coupling Reactions. To a mixture of 4-(o-iodo-
phenyl)-1-butyne (0.77 g, 3 mmol) in 5 ml of THF were sequentially added
Pd(PPh3)2 (0.17 g, 0.15 mmol) in 2 ml of THF and 2-pyridylzinc chloride solution, prepared by mixing 2-pyridyllithium15 (9 ml of 1 N in THF) and zinc chloride solution (9 ml of 1 N in THF) at 0°C, over a period of 2 h. The reaction mixture was then stirred at room temperature for another 8 h. The reaction mixture was quenched by adding water (10 ml) at 0°C and the organic layer was extracted with diethyl ether (20 ml x 3). The combined organic layer was washed with water (10 ml) and brine (10 ml), dried over magnesium sulfate, filtered, concentrated, and purified by column chromatography (hexane/ether = 10/1) to give 2 (0.41 g, 1.98 mmol) as a colorless liquid in 66% yield and trace (<2%) amount of the uncyclized product 2-[2-(3-butylnyl)phenyl]pyridine. 2:

'H-Nmr (CDCl3, TMS) δ 2.9-3.1 (m, 4 H), 6.63 (s, 1 H), 7.03 (dt, J = 0.7, 7.8 Hz, 1 H), 7.1-7.3 (m, 3 H), 7.39 (d, J = 7.8 Hz, 1 H), 7.64 (dt, J = 1.8, 7.8 Hz, 1 H), 7.77 (d, J = 7.8 Hz, 1 H), 8.64 (d, J = 4.8 Hz, 1 H) ppm. 13C-Nmr (CDCl3, TMS) δ 29.96, 35.01, 120.86, 121.15, 123.64, 125.07, 125.34, 125.68, 128.72, 135.89, 146.87, 149.17, 156.75 ppm. Ir (neat) ν 1580, 1425, 755 cm⁻¹. Ms m/z 207 (M⁺). Hrms calcd for C19H13N: 207.1048, found 207.1048. Anal. Calcd for C19H13N: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.68; H, 6.09; N, 6.98.

(Z)-3-(1-Indanylidenemethyl)pyridine 3: 53% Yield. Colorless oil. 1H-Nmr
(CDCl3, TMS) δ 2.9-3.1 (m, 4 H), 6.52 (s, 1 H), 6.95 (t, 7.2 Hz, 1 H), 7.1-7.3 (m, 4 H), 7.69 (d, J = 7.5 Hz, 1 H), 8.51 (dd, J = 1.7, 4.8 Hz, 1 H), 8.6-8.7
(m, 1 H) ppm. \(^{13}\)C-Nmr (CDCl\(_3\), TMS) \& 30.02, 34.18, 117.13, 123.11, 123.91, 125.44, 125.88, 128.55, 134.03, 135.74, 138.97, 145.79, 147.68, 148.94, 149.70 ppm. Ir (neat) \& 765, 710 cm\(^{-1}\). Ms m/z 207 (M'). Hrms calcd for C\(_{13}\)H\(_{13}\)N 207.1048, found 207.1038. Anal. Calcd for C\(_{13}\)H\(_{13}\)N: C, 86.92; H, 6.32; N, 6.76. Found: C, 86.65; H, 6.01; N, 6.82.

(Z)-2-(1-Indanyldienemethyl)furan 4: 58% Yield. Colorless oil. \(^{1}\)H-Nmr (CDCl\(_3\), TMS) \& 2.8-3.1 (m, 4 H), 6.3-6.4 (m, 2 H), 6.4-6.5 (m, 1 H), 7.1-7.3 (m, 3 H), 7.45 (t, J = 0.7 Hz, 1 H), 8.1-8.2 (m, 1 H) ppm. \(^{13}\)C-Nmr (CDCl\(_3\), TMS) \& 29.95, 35.33, 108.89, 109.03, 111.18, 124.92, 126.08, 128.29, 139.06, 140.91, 142.44, 148.92, 152.35 ppm. Ir (neat) \& 765, 725 cm\(^{-1}\). Ms m/z 196 (M'). Hrms calcd for C\(_{14}\)H\(_{12}\)O 196.0888, found 196.0884. Anal. Calcd for C\(_{14}\)H\(_{12}\)O: C, 85.68; H, 6.16. Found: C, 85.37; H, 6.28.

(Z)-2-(1-Indanyldienemethyl)thiophene 5: 74% Yield. Colorless oil. \(^{1}\)H-Nmr (CDCl\(_3\), TMS) \& 2.9-3.0 (m, 4 H), 6.53 (br s, 1 H), 7.0-7.1 (m, 3 H), 7.17 (dt, J = 1.1, 7.5 Hz, 1 H), 7.2-7.3 (m, 2 H), 7.49 (d, J = 7.8 Hz, 1 H) ppm. \(^{13}\)C-Nmr (CDCl\(_3\), TMS) \& 29.97, 34.13, 113.10, 124.33, 124.47, 125.19, 125.73, 125.83, 127.02, 128.40, 139.15, 140.32, 145.83, 148.79 ppm. Ir (neat) \& 850, 755, 695 cm\(^{-1}\). Ms m/z 212 (M'). Hrms calcd for C\(_{14}\)H\(_{12}\)S 212.0660, found 212.0663. Anal. Calcd for C\(_{14}\)H\(_{12}\)S: C, 79.20; H, 5.70. Found: C, 79.03; H, 5.51.
2-[2-(3-Butynyl)phenyl]furan 8: 28% Yield. Colorless oil. \( ^1H \)-Nmr (CDCl\textsubscript{3}, TMS) \( \delta 1.98 \) (t, \( J = 2.6 \) Hz, 1 H), 2.47 (dt, \( J = 2.6, 7.5 \) Hz, 2 H), 3.07 (t, \( J = 7.5 \) Hz, 2 H), 6.4-6.5 (m, 2 H), 7.2-7.3 (m, 3 H), 7.5-7.6 (m, 2 H) ppm. \( ^{13}C \)-Nmr (CDCl\textsubscript{3}, TMS) \( \delta 19.72, 33.25, 68.68, 83.86, 108.04, 111.18, 126.52, 127.60, 128.23, 129.93, 130.25, 131.29, 153.47 \) ppm. Ir (neat) \( \nu 3300, 1010, 760, 740, 640 \) cm\textsuperscript{-1}. Ms m/z 196 (M\textsuperscript{+}). Hrms calcd for C\textsubscript{14}H\textsubscript{10}O: 196.0888, found 196.0878. Anal. Calcd for C\textsubscript{14}H\textsubscript{10}O: C, 85.68; H, 6.16. Found: C, 85.47; H, 6.29.

2-[2-(3-Butynyl)phenyl]thiophene 9: 6% Yield. Colorless oil. \( ^1H \)-Nmr (CDCl\textsubscript{3}, TMS) \( \delta 1.95 \) (t, \( J = 2.6 \) Hz, 1 H), 2.39 (dt, \( J = 2.6, 7.2 \) Hz, 2 H), 2.98 (t, \( J = 7.2 \) Hz, 2 H), 7.0-7.1 (m, 2 H), 7.2-7.4 (m, 5 H) ppm. \( ^{13}C \)-Nmr (CDCl\textsubscript{3}, TMS) \( \delta 20.01, 32.39, 68.78, 83.66, 125.34, 126.34, 126.44, 127.01, 128.05, 129.59, 131.19, 133.94, 138.73, 142.21 \) ppm. Ir (neat) \( \nu 3300, 760, 700, 640 \) cm\textsuperscript{-1}. Ms m/z 212 (M\textsuperscript{+}). Hrms calcd for C\textsubscript{14}H\textsubscript{10}S: 212.0661, found 212.0660. Anal. Calcd for C\textsubscript{14}H\textsubscript{10}S: C, 79.20; H, 5.70. Found: C, 79.01; H, 5.52.

2-(2-(3-Butynyl)phenyl)-N-methylpyrrole 10: 33% Yield. Colorless oil. \( ^1H \)-Nmr (CDCl\textsubscript{3}, TMS) \( \delta 1.91 \) (t, \( J = 2.6 \) Hz, 1 H), 2.29 (dt, \( J = 2.6, 7.4 \) Hz, 2 H), 2.76 (t, \( J = 7.4 \) Hz, 2 H), 3.38 (s, 3 H), 6.07 (dd, \( J = 1.8, 3.6 \) Hz, 1 H), 6.20 (dd, \( J = 1.8, 2.7 \) Hz, 1 H), 6.70 (dd, \( J = 1.8, 2.7 \) Hz, 1 H), 7.2-7.4 (m, 4 H) ppm. \( ^{13}C \)-Nmr (CDCl\textsubscript{3}, TMS) \( \delta 19.53, 32.24, 34.05, 68.64, 83.82, 107.27, 108.68, 121.64, 126.02, 128.03, 129.19, 131.54, 132.08, 132.78, 140.51 \) ppm. Ir (neat) \( \nu 3300, 1475, 1310, 760, 710, 640 \) cm\textsuperscript{-1}. Ms m/z 209 (M\textsuperscript{+}). Hrms calcd for C\textsubscript{15}H\textsubscript{12}N: 209.1204, found 209.1206. Anal. Calcd for C\textsubscript{15}H\textsubscript{12}N: C, 86.09; H, 7.22; N, 6.69. Found: C, 85.97; H, 7.20; N, 6.85.

2-[2-(3-Butynyl)phenyl]benzothiazole 11: 21% Yield. Colorless oil. \( ^1H \)-Nmr (CDCl\textsubscript{3}, TMS) \( \delta 1.95 \) (t, \( J = 2.7 \) Hz, 1 H), 2.59 (dt, \( J = 2.7, 7.5 \) Hz, 2 H), 3.29 (t, \( J = 7.5 \) Hz, 2 H), 7.3-7.6 (m, 5 H), 7.71 (d, \( J = 7.2 \) Hz, 1 H), 7.94 (d, \( J = 7.8 \) Hz, 1 H), 8.10 (d, \( J = 8.4 \) Hz, 1 H) ppm. \( ^{13}C \)-Nmr (CDCl\textsubscript{3}, TMS) \( \delta 20.21, 32.87, 68.74, 83.96, 121.26, 123.47, 125.12, 126.06, 126.74, 129.95, 132.78, 131.11, 132.68, 135.45, 139.60, 153.89 \) ppm. Ir (neat) \( \nu 3300, 1435, 960, 760, 710, 640 \) cm\textsuperscript{-1}. Ms m/z 263 (M\textsuperscript{+}). Hrms calcd for C\textsubscript{17}H\textsubscript{13}NS: 263.0769, found 263.0771. Anal. Calcd for C\textsubscript{17}H\textsubscript{13}NS: C, 77.53; H, 4.97; N, 5.32. Found: C, 77.40; H, 4.73; N, 5.50.
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