Research Article

Phosphine-Free Palladium-Catalyzed Direct C-3 Arylation of 2-Phenylimidazo[1,2-a]pyridine Using Silver(I) Carboxylate

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Phosphine-free palladium-catalyzed direct arylation of 2-phenyl-imidazo[1,2-a]pyridine has been developed with the concept of using silver(I) carboxylate. This protocol efficiently catalyzes the C-H arylation of 2-phenyl-imidazo[1,2-a]pyridine with aryl iodides to afford the corresponding 2-phenyl-3-aryl-imidazo[1,2-a]pyridines in moderate to good yields.

1. Introduction

Syntheses of several heterocycles via palladium-catalyzed direct C-H bond activation using aryl halides are of great importance in recent years along with time-honored coupling reactions where expensive and toxic phosphines are widely used [1–6]. Hence, there are significant efforts to perform reactions without using any phosphines for the same reasons. In this aspect, phosphine-free palladium-catalyzed synthesis of free (N-H) as well as substituted indole and pyrroles are reported in the literature [7–9]. In 2008, Igor Larosa reported the intrinsic idea of using the several different types of Ag(I) carboxylate salts (generated in situ by the combination of Ag2O/different substituted benzoic acids) along with Pd(OAc)2 to undergo C-H bond activation under very mild conditions to afford C-2 arylated indoles with different functionalities [9]. This paper prompted us to use the same approach for the highly demanding arylation for the C3 position of imidazo[1,2-a]pyridine, a heterocycle with outstanding biological activities [10–15]. The most well known drugs like zolimidine (A, antiulcer), alpidem (B, anxiolytic), and zolpidem (C, hypnotic) [14] (Figure 1) also bear this imidazo[1,2-a]pyridine skeleton.

It is to be noted that, in 2007, the research group of Dalibor reported the phosphine-free Pd(OAc)2 catalyzed direct C-arylation of free (–NH) indoles and pyrroles in the presence of CsOAc [8]. Recently there are few reports on the Pd-catalyzed direct C-3 arylation of imidazo[1,2-a]pyridines using phosphines as ligands [16–19] along with the traditional coupling reactions where the starting material should be 3-haloimidazo[1,2-a]pyridines [20–23]. During the preparation of our paper, Fu and collaborators published the phosphine-free Pd-catalyzed direct arylation of imidazo [1,2-a]pyridine using KOAc as base [24]. However, prior to the work published by Fu et al. to the best of our knowledge, there was no report on the phosphine-free direct arylation of imidazo[1,2-a]pyridine using palladium as catalyst. In this present work, we describe a new convenient methodology for the phosphine-free direct C3 alkylation of 2-phenylimidazo[1,2-a]pyridine by the reaction of aryl iodides in the presence of Pd(OAc)2 as catalyst with silver(I) carboxylate which is assumed to increase the rate of the palladation step in the catalytic cycle along with its basic nature needed at the reductive elimination step [9]. This methodology also offer a new route for the direct arylation of 2-phenylimidazo[1,2-a]pyridine with aryl iodides.
2. Experimental

2.1. General. All the chemicals used were purchased from Aldrich Chemical Co. and were used without further purification. Freshly distilled solvents were used. For TLC, aluminum plates coated with silica gel containing F254 indicator were used and the spots were visualized by UV light and/or by exposing to iodine. Column chromatography was performed on silica gel 100–200 mesh, using EtOAc and hexanes mixture as eluent. The $^1$H and $^{13}$C NMR spectra were recorded using 5 mm tubes on a Bruker 500 MHz NMR spectrometer (field strengths: 500 and 125 MHz, resp.) or 400 MHz NMR spectrometer (field strengths: 400 and 100 MHz resp.) in CDCl$_3$ solution (unless specified otherwise) with shifts referenced to SiMe$_3$ ($^1$H, $^{13}$C: δ = 0). All $^1$J values were in Hz. IR spectra were recorded on a JASCO FT/IR 3500 spectrometer. Elemental (C, H, N) analysis was done using Perkin-Elmer 2400 CHN FLASH EA analyzer. Melting points were determined by using a SUPERFIT hot-stage melting point apparatus and are uncorrected.

2.2. General Procedure for the Synthesis of 2-Phenylimidazo[1,2-$a$]pyridine (1). To the solution of 2-aminopyridine (5 mmol) in ethanol (30 mL), 2-bromo acetophene (2.0 mmol), Pd(OAc)$_2$ (5 mmol) in ethanol (30 mL), Ag$_2$O (174 mg, 0.75 mmol), and 2-nitrobenzoic acid (251 mg, 1.5 mmol) was stirred at 120°C for 12 h under nitrogen in DMF. The reaction mixture was filtered through a plug of silica gel and then evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (Hexane:EtOAc 80:20) to afford 2,3-diphenylimidazo[1,2-$a$]pyridine. For the synthesis of compounds 3b-k: similar molar quantities of the respective aryl iodides were used with 1.0 mmol of 2-phenylimidazo[1,2-$a$]pyridine.

2.3. General Procedure for the Direct Arylation of 2-Phenylimidazo[1,2-$a$]pyridine. A mixture of 2-phenylimidazo[1,2-$a$]pyridine (194 mg, 1.0 mmol), iodobenzene (224 µL, 2.0 mmol), Pd(OAc)$_2$ (11.2 mg, 5 mol%), Ag$_2$O (174 mg, 0.75 mmol), and 2-nitrobenzoic acid (251 mg, 1.5 mmol) was stirred at 120°C for 12 h under nitrogen in DMF. The reaction mixture was filtered through a plug of silica gel and then evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (Hexane:EtOAc 80:20) to afford 2,3-diphenylimidazo[1,2-$a$]pyridine. For the synthesis of compounds 3b-k: similar molar quantities of the respective aryl iodides were used with 1.0 mmol of 2-phenylimidazo[1,2-$a$]pyridine.
112.7, 117.9, 119.9, 123.1, 125.2, 127.9, 128.4, 129.5, 130.6, 133.8, 134.8, 137.0, 143.6, 145.3. IR (νmax, cm⁻¹): 3053, 1684, 1605, 1267, 958, 698 LC/MS, m/z 313 [M + 1]; Calcld. for C21H16N2O: C, 80.75; H, 5.16; N, 8.97%. Found: C, 80.65; H, 5.21; N, 8.86%.

2-Phenyl-3-(3,4,5-trimethoxyphenyl)imidazo[1,2-alpyridine (3f). Colorless solid, Yield 86%, 0.31 g, Mp 122–124°C; 1H NMR (400 MHz, CDCl₃): δH 2.48 (s, 3H, CH₃), 6.73 (td, 3J(H-H) = 7.0 Hz, 1.0 Hz, 1H, Ar-H), 7.19–7.36 (m, 8H, Ar-H), 7.69–7.72 (m, 3H, Ar-H), 7.96 (d, 3J(H-H) = 7.0 Hz, 1H, Ar-H). 13C NMR (100 MHz, CDCl₃): δC 21.5, 112.2, 117.5, 121.3, 123.4, 124.7, 127.5, 127.9, 128.0, 128.3, 129.5, 129.7, 131.2, 134.1, 139.3, 142.1, 144.7. IR (νmax, cm⁻¹): 2920, 1601, 1537, 1469, 1457, 1377. IR (νmax, cm⁻¹): 3063, 1599, 1566, 1105, 854, 736. LC/MS, m/z 285 [M + 1]+; Anal. Calcld. for C₂₁H₁₈N₂O: C, 84.48; H, 5.67; N, 8.95%. Found: C, 84.58; H, 5.61; N, 9.75%.

3-(4-Nitrophenyl)-2-phenylimidazo[1,2-alpyridine (3h). Yellow-colored solid, Yield 89%, 0.28 g, Mp 150–152°C; 1H NMR (500 MHz, CDCl₃): δH 6.86–6.88 (m, 1H, Ar-H), 7.28–7.36 (m, 4H, Ar-H), 7.59–7.60 (m, 2H, Ar-H), 7.68 (d, 3J(H-H) = 9.0 Hz, 2H, Ar-H), 7.75 (d, 3J(H-H) = 9.0 Hz, 1H, Ar-H), 8.11 (dd, 3J(H-H) = 7.0 Hz, 1H, Ar-H), 8.38 (d, 3J(H-H) = 8.5 Hz, 2H, Ar-H). 13C NMR (125 MHz, CDCl₃): δC 111.2, 128.1, 118.8, 122.8, 124.7, 125.6, 128.2, 128.5, 128.6, 131.1, 133.5, 136.6, 144.5, 145.7, 147.5. IR (νmax, cm⁻¹): 3063, 1599, 1566, 1105, 854, 736. LC/MS, m/z 316 [M + 1]+; Anal. Calcld. for C₁₉H₁₄N₂O: C, 72.37; H, 4.16; N, 13.33%. Found: C, 72.34; H, 4.23; N, 13.21%.

3-(3,5-Dimethylphenyl)-2-diphenylimidazo[1,2-alpyridine (3l). Colorless solid, Yield 84%, 0.25 g, Mp 158–160°C; 1H NMR (400 MHz, CDCl₃): δH 2.39 (s, 6H, CH₃), 6.74 (td, 3J(H-H) = 6.4 Hz, 1.2 Hz, 1H, Ar-H), 7.08 (s, 2H, Ar-H), 7.14 (s, 1H, Ar-H), 7.18–7.35 (m, 4H, Ar-H), 7.67–7.74 (m, 3H, Ar-H), 7.94 (d, 3J(H-H) = 6.8 Hz, 1H, Ar-H). 13C NMR (100 MHz, CDCl₃): δC 21.4, 112.1, 117.4, 121.4, 123.5, 124.5, 127.4, 127.9, 128.2, 128.3, 129.7, 130.7, 134.3, 139.2, 142.0, 144.7. IR (νmax, cm⁻¹): 2920, 1601, 1444, 1342, 752, 702. LC/MS, m/z 299 [M + 1]+; Anal. Calcld. for C₃₂H₂₃N₂: C, 84.53; H, 6.08; N, 9.39%. Found: C, 84.45; H, 6.15; N, 9.45%. 3-(2-Nitrophenyl)-2-phenylimidazo[1,2-alpyridine (3j). Yellow-colored solid, Yield 76%, 0.24 g, Mp 154–156°C; 1H NMR (400 MHz, CDCl₃): δH 6.83–6.87 (m, 1H, Ar-H), 7.27–7.35 (m, 4H, Ar-H), 7.56–7.67 (m, 4H, Ar-H), 7.73 (d, 3J(H-H) = 8.8 Hz, 1H, Ar-H), 8.09 (d, 3J(H-H) = 8.8 Hz, 1H, Ar-H), 8.38 (d, 3J(H-H) = 8.5 Hz, 2H, Ar-H). 13C NMR (100 MHz, CDCl₃): δC 111.2, 118.1, 118.8, 122.8, 124.7, 125.6, 128.1, 130.5, 136.7, 139.4, 145.7, 147.5. IR (νmax, cm⁻¹): 2924, 1528, 1352, 851, 750. LC/MS, m/z 316 [M + 1]+; Anal. Calcld. for C₁₈H₁₃N₂O₂: C, 72.37; H, 4.16; N, 13.33%. Found: C, 72.41; H, 4.26; N, 13.26%.

3. Results and Discussion

Using Pd(OAc)₂ as catalyst and several different types of silver(I) acetates or carboxylates, we have begun phosphine-free reactions of 2-phenylimidazo[1,2-alpyridine (1) with phenyl iodide to afford the direct C-3 arylated product 2,3-diphenyl imidazo[1,2-alpyridine (2a) (Scheme 1). We have taken this reaction as a model to optimize the yield by changing different combinations of Ag(I) carboxylate (generated in situ from Ag₂O and different carboxylic acids) along with other bases and solvents (Table 1). Indeed, compound 1 is a very stable starting material that could be synthesized in a convenient way by the reaction of cheap commercially available 2-aminoypyridine and 2-bromoacetophenone. Moreover, 2-phenylimidazo[1,2-alpyridine derivatives are well established as potent and selective ligands for peripheral benzodiazepine receptor [10].

There was no progress of this reaction at room temperature. The highly coordinating dimethylformamide (DMF) was the best choice as a solvent for the reaction of commercially available 2-aminoypyridine and 2-bromoacetophenone. Therefore, 2-phenylimidazo[1,2-alpyridine derivatives are well established as potent and selective ligands for peripheral benzodiazepine receptor [10].

It is experimental that the percentages of yields do not vary considerably (entries 2, 4, 5, and 6) with the type of substituents present (or absent; entry 1) in the phenyl ring of aryl iodides. Both, electron-withdrawing (entries 4, 5, 8, and 10) and electron-donating substituents (entries 2, 3, 6, 7, and 9) show the same result. As expected, the more hindered ortho-substituted aryl iodides react considerably more slowly than the meta- and para-counterparts to afford slightly lower yields (entries 7 and 10). Further, we also have checked the reactivity of 2-iodothiophene as a heteroaryl iodide under the same reaction condition which affords the compound 3k with 66% yield. All the compounds (3a–k) were characterized by IR, NMR, mass spectroscopy, and elemental analysis. In the 1H-NMR spectra all aromatic protons resonate in the
Scheme 1: Pd(OAc)$_2$ catalyzed reaction of 2-phenylimidazo[1,2-a]pyridine with aryl iodides in the presence of Ag(I) carboxylate salts.

**Table 1: Optimization of the coupling between 2-phenylimidazo[1,2-a]pyridine (1) and phenyl iodide.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Acid</th>
<th>Solvent</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$</td>
<td>None</td>
<td>DMF</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$CO$_3$</td>
<td>CH$_3$CO$_2$H</td>
<td>DMF</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$</td>
<td>o-O$_2$N-C$_6$H$_4$-CO$_2$H</td>
<td>DMF</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>Ag$_2$O</td>
<td>None</td>
<td>DMF</td>
<td>Trace</td>
</tr>
<tr>
<td>5</td>
<td>Ag$_2$O</td>
<td>CH$_3$CO$_2$H</td>
<td>DMF</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>Ag$_2$O</td>
<td>o-O$_2$N-C$_6$H$_4$-CO$_2$H</td>
<td>DMF</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>Ag$_2$O</td>
<td>o-O$_2$N-C$_6$H$_4$-CO$_2$H</td>
<td>Dioxane</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>Ag$_2$O</td>
<td>o-O$_2$N-C$_6$H$_4$-CO$_2$H</td>
<td>Dioxane-EtOH</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>Ag$_2$O</td>
<td>CF$_3$CO$_2$H</td>
<td>Dioxane</td>
<td>38</td>
</tr>
</tbody>
</table>

All reactions were carried out using 5 mol% Pd(OAc)$_2$, 1.5 equiv (entries 1–3), or 0.75 equiv (entries 4–8) of base, 1.5 equiv of acid, 1.0 equiv of 1, and 2.0 equiv of phenyl iodide in a 0.5 M solution, for 12 h at 120$^\circ$C.

**Figure 2:** Molecular structure of the compound 3c (entry 3). (X-ray data was collected on a Bruker AXS-SMART diffractometer using Mo-K$_\alpha$ ($\lambda = 0.71073$ Å) radiation. The structure was solved and refined by standard methods. Crystal data for 3c: C$_{20}$H$_{16}$N$_2$, M = 284.35, Monoclinic, Space group P2(1)/n, a = 7.4312(15), b = 11.708(2), c = 17.611(4) Å, $\alpha = 90.00^\circ$, $\beta = 95.36(3)^\circ$, $\gamma = 90.00^\circ$, $V = 1525.6(5)$ Å$^3$, $Z = 4$, $\mu = 0.073$ mm$^{-1}$, data/restraints/parameters: 2677/0/200, R indices ($I > 2(I)$): R1 = 0.0513, wR2 (all data) = 0.1208. CCDC no. 885064).

4. Conclusions

In conclusion, we have applied the catalytic Pd(OAc)$_2$ and Ag(I) carboxylate combination to develop a successful methodology for this challenging direct C-3 arylation of 2-phenylimidazo[1,2-a]pyridine with differently substituted aryl iodides without the presence of phosphines or other ligands to give 3-aryl-2-phenylimidazo[1,2-a]pyridines with moderate to-high yield. The structure of one of these compounds has been characterized by X-ray crystallography.
**Table 2: Direct arylation of 2-phenylimidazo[1,2-α]pyridine (1) with differently substituted aryl iodides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Products</th>
<th>Yield (isolated, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image" alt="Product 3a" /></td>
<td>82</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image" alt="Product 3b" /></td>
<td>81</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image" alt="Product 3c" /></td>
<td>78</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image" alt="Product 3d" /></td>
<td>90</td>
</tr>
<tr>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image" alt="Product 3e" /></td>
<td>85</td>
</tr>
<tr>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image" alt="Product 3f" /></td>
<td>86</td>
</tr>
<tr>
<td>7&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image" alt="Product 3g" /></td>
<td>51</td>
</tr>
</tbody>
</table>

<sup>a</sup> Synthesis conditions: 5 mol% Pd(OAc)<sub>2</sub>, 0.75 equiv Ag<sub>2</sub>O, 1.5 equiv o-N<sub>2</sub>C<sub>6</sub>H<sub>4</sub>-COOH, DMF, 120°C.
TABLE 2: Continued.

\[
\begin{align*}
\text{N} & \quad \text{N} + \text{N} \quad \text{Ar} \\
5 \text{ mol\% Pd(OAc)}_2 & , \\
0.75 \text{ equiv Ag}_2\text{O}, & \\
1.5 \text{ equiv o-O} & \text{N–C}_6\text{H}_4–\text{COOH} \\
\text{DMF, } 120^\circ\text{C} & \\
\rightarrow & \\
\text{N} & \quad \text{N} \quad \text{Ar} \\
1 & \quad 3a-k
\end{align*}
\]

\[8^a \quad 89\]

\[9^a \quad 84\]

\[10^b \quad 76\]

\[11^b \quad 66\]

The reaction was carried out for 12h. \(^b\)The reaction was carried out for 24h.

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**References**


[10] G. Trapani, M. Franco, A. Latrofa et al., “Novel 2-phenylimidazo[1,2-α]pyridine derivatives as potent and selective ligands for peripheral benzodiazepine receptors:


