PALLADIUM CATALYZED MONO- AND DIARYLATION OF 2-METHYLQUINOLINES

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ABSTRACT:
Reactions of 2-methylquinolines with aryl iodides in the system Pd(OAc)$_2$ (5 mol.%) / dppb (1,4-bis(diphenylphosphino)butane) (10 mol.%) / t-BuOK (1.3 eq.) in toluene afforded mono- and diarylated products in yields up to 44 %.

Keywords: Palladium catalyst, 2-methylquinolines, 2-benzyl-6-methoxy-quinoline, 6-Methoxy-2-(diphenylmethyl)quinoline, 6-methoxy-2-(4-methoxybenzyl)quinoline

INTRODUCTION
Benzylquinolines and diarylmethylquinolines are of interest as valuable intermediates in organic synthesis. Usually benzylquinolines were obtained by reaction of benzyl sodium with quinoline$^1$, benzyl magnesium bromide with quinoline$^2$, methylquinoline with chlorobenzene$^3$ or by homolytic benzylation of quinoline with toluene derivatives$^4$.

Diarylmethylquinolines were obtained from quinoline and benzene in the presence of dehydrating agent (for example, H$_2$SO$_4$)$^5$ or from quinoline aldehyde and benzene in the presence of triflic acid$^6$.

Palladium catalyzed arylation reactions of ketones, amides and related nucleophiles were recently described in some reviews$^7$-$^9$. The best catalytic systems for arylation of ketone enolates were found to be Pd$_2$(dba)$_3$ / BINAP / t-BuONa$^{10}$, Pd$_2$(dba)$_3$ / Tol-BINAP / t-BuONa / THF$^{11}$, Pd(OAc)$_2$ / Xantphos / t-BuONa or K$_3$PO$_4$$^{12}$, Pd(OAc)$_2$ / PPh$_3$ / Cs$_2$CO$_3$ / DMF$^{13}$, Pd(OAc)$_2$ / RR$_3$ (R= alkyl, aryl) / Cs$_2$CO$_3$$^{14}$ and (imidazol-2-ylidene)palladium acetate / t-BuONa / dioxane$^{15}$. Palladium catalyzed arylation of nitrites$^{16}$ and sulfones$^{17}$ were described too. Recently was described simple arylation of 8-methylquinoline with 4-bromo-1-iodobenzene to corresponding benzylquinoline in the system Pd(OAc)$_2$ / AgOAc / AcOH$^{18}$. However, only mono-arylated products were obtained in the above system. Recently we reported our first results in Pd-catalyzed mono- and diarylation of methylquinolines.$^{19}$ Now we are presenting a novel Pd-catalyzed method of synthesis of benzylquinolines and diarylmethylquinolines.

RESULTS AND DISCUSSION
We have developed a new and simple palladium catalyzed arylation method of methylquinolines. The influence of catalyst, base and solvent was studied in the arylation
reaction of 2-methylquinoline (1) with iodobenzene (2 eq.). Interestingly, the system Pd(OAc)$_2$ (5 mol.%) / dppb (1,4-bis(diphenylphosphino)butane) (10 mol.%) / t-BuOK (1.3 eq.) in toluene was found to be the most active for the diarylation of compound 1. In this system compound 3 was obtained in the 41% yield, along with mono-arylated product 2 (17%). Increase in the amount of t-BuOK to 2.6 equiv. and using P(o-Tol)$_3$ as ligand diminishes the yields of products 2 and 3. The systems Pd(OAc)$_2$ (5 mol.%) / Cul (10 mol.%) / t-BuOK / toluene, Pd(OAc)$_2$ (5 mol.%) / dppb (10 mol.%) / t-BuOK (1.3 eq.) / CsOH (1.3 eq.) / 18-crown-6 (10 mol.%) / toluene and Pd(PPh$_3$)$_4$ (5mol.%) / t-BuOK (1.3 eq.) / toluene were essentially inactive in the arylation of compound 1 (Table 1).

![Chemical structures](image.png)

**Table 1. Palladium catalyzed arylation of 2-methylquinoline (1) with 2 equivalent of PhI at 100°C for 48 h.**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield of 2, % (GC-MS data)</th>
<th>Yield of 3, % (GC-MS data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(OAc)$_2$ (5 mol.%)</td>
<td>Dppb (10 mol.%)</td>
<td>t-BuOK (1.3 eq.)</td>
<td>Toluene</td>
<td>17</td>
<td>41</td>
</tr>
<tr>
<td>Pd(OAc)$_2$ (2.5 mol.%)</td>
<td>Dppb (5 mol.%)</td>
<td>t-BuOK (1.3 eq.)</td>
<td>Toluene</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Pd(OAc)$_2$ (5 mol.%)</td>
<td>Dppb (10 mol.%)</td>
<td>t-BuOK (2.6 eq.)</td>
<td>Toluene</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Pd(OAc)$_2$ (5 mol.%)</td>
<td>Dppb (10 mol.%)</td>
<td>t-BuOK (1.3 eq.)</td>
<td>DMF</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Pd(OAc)$_2$ (5 mol.%)</td>
<td>Dppb (10 mol.%)</td>
<td>CsOH (1.3 eq.) + 18-crown-6 (10 mol.%)</td>
<td>Toluene</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pd(OAc)$_2$ (5 mol.%)</td>
<td>P(o-Tol)$_3$ (10mol.%)</td>
<td>t-BuOK (1.3 eq.)</td>
<td>Toluene</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Pd(OAc)$_2$ (5 mol.%)</td>
<td>Dppb (10mol.%)</td>
<td>t-BuOK (1.3 eq.)</td>
<td>Toluene</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pd(PPh$_3$)$_4$ (5 mol.%)</td>
<td>-</td>
<td>t-BuOK (1.3 eq.)</td>
<td>Toluene</td>
<td>Traces</td>
<td>0</td>
</tr>
</tbody>
</table>
The catalytic system system Pd(OAc)$_2$ (5 mol.%) / dppb (1,4-bis(diphenylphosphino)butane) (10 mol.%) / $t$-BuOK (1.3 eq.) in toluene, as the most active, was used in the arylation of 2-methyl-6-methoxyquinoline (4) with iodobenzene or 1-iodo-4-methoxybenzene.

Arylation of quinoline 4, having electrondonating group in the position 6, with iodobenzene in above system leads to mixture of mono- (5) (yield 12%) and diarylated product (6) (yield 13%). However, reaction of compound 4 with 1-iodo-4-methoxybenzene was selective so that 6-methoxy-2-(4-methoxybenzyl)quinoline (7) was isolated in 44 % yield as single product. Diarylation of compound 4 in this case did not occurred due to deactivation of methylene group in the compound 7 by methoxy group in para-position.

Thus, palladium catalyzed arylation of methylquinolines is a simple method for the synthesis of benzylquinolines and diarylmethylquinolines which otherwise are difficult to obtain.

**EXPERIMENTAL SECTION**

$^1$H spectra were recorded on a Varian Mercury BB 400 MHz in CDCl$_3$ using HMDS as internal standard. Mass spectra were registered on a GC-MS HP 6890 (70 eV).

**General procedure for the arylation of 2-methylquinoline with iodobenzene in the presence of palladium catalyst**

2-Methylquinoline (0.14 ml, 1 mmol), iodobenzene (0.22 ml, 2 mmol) and base (see Table 1) were added to stirred solution of palladium catalyst and ligand (see Table 1) in dry toluene (1.25 ml) in a Pierce reacti-vial (5 ml) under argon atmosphere. The mixture was stirred at 100$^\circ$C (GC-MS control) for 48 h, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: toluene: ethyl acetate 10:1) to obtain desired products 2 and 3 $^5,^6$ as colorless oils (see Table 1).

**General procedure for the arylation of 2-methyl-6-methoxyquinoline (4) with iodobenzene or 1-iodo-4-methoxybenzene in the presence of palladium catalyst.**

2-Methyl-6-methoxyquinoline (4) (0.224 g, 1 mmol), aryl iodide (2 mmol) and $t$-BuOK (0.146 g, 1.3 mmol) were added to stirred solution of Pd(OAc)$_2$ (0.011 g, 0.05 mmol) and 1,4-bis(diphenylphosphino)butane (dppb) (0.043 g, 0.1 mmol) in dry toluene (1.25 ml) in a Pierce reacti-vial (5 ml) under argon atmosphere. The mixture was stirred at 100$^\circ$C (GC-MS control) for 48 h, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: toluene: ethyl acetate 10:1) to obtain desired products 5-7 as colourless oils.
The properties of obtained products were as follows:

2-Benzyl-6-methoxy-quinoline (5). Yield 12 %. $^1$H NMR δ (ppm): 3.91 (s, 3H, Me), 4.30 (s, 2H, CH$_2$), 7.02-7.38 and 7.90-8.00 (both m, 10H, Ph and quinoline ring protons). MS: m/z (%): 249 (M$^+$, 58), 248 (100), 234 (10), 205 (21).

6-Methoxy-2-(diphenylmethyl)quinoline (6). Yield 13 %. $^1$H NMR δ (ppm): 3.91 (s, 3H, Me), 5.87 (s, 1H, CH), 7.03-7.31 and 7.93-7.97 (both m, 15H, Ph and quinoline ring protons). MS: m/z (%): 326 (M$^+$, 15), 324 (100), 281 (16), 204 (26), 165 (33), 152 (13).

6-Methoxy-2-(4-methoxybenzyl)quinoline (7). Yield 44 %. $^1$H NMR δ (ppm): 3.76 (s, 3H, MeO in Ph ring) 3.91 (s, 3H, MeO in quinoline ring), 4.23 (s, 2H, CH$_2$), 6.81-7.37 and 7.89-7.99 (both m, 9H, Ph and quinoline ring protons). MS: m/z (%): 279 (M$^+$, 98), 278 (100), 264 (66), 221 (11), 192 (12), 121 (14).

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