Palladium-catalysed arylation of acetoacetate esters to yield 2-arylacetic acid esters

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Abstract—The coupling reaction between ethyl acetoacetate and a number of aryl halides in the presence of palladium acetate, a bulky and electron rich phosphine and K3PO4 is described. The arylated acetoacetate ester is de-acylated under the reaction conditions resulting in the generation of 2-arylacetic acid esters, constituting a mild alternative to direct arylation of carboxylate esters.

The preparation of 2-arylalkanoic acid derivatives especially arylpropionic acids has received significant attention during the past few decades since they find application as nonsteroidal anti-inflammatory drugs (NSAID) (Fig. 1).1 Arylation of β-dicarbonyl carbanions has been investigated as a synthetic strategy to obtain 2-arylactic or arylpropionic acids. For example, the preparation of ibuprofen by way of arylation of methylmalonic acid esters using an arylead tricarboxylic acid was established many years ago.2 More recently the copper-catalysed arylation of ethyl cyanoacetate and diethyl malonate has also been demonstrated, using aryl iodides.3 However, the palladium-catalysed enolate arylation reaction for the preparation of 2-arylalkanoic acid derivatives has probably received the most attention. This chemistry has been mainly developed by the groups of Hartwig and Buchwald.4,5 Two strategies in this regard, leading to arylpropionic acids have recently been published: (a) palladium-catalysed arylation of diethyl malonate followed by methylation,4,6 and (b) direct palladium-catalysed arylation of propionic or acetic acid esters.5 The arylation of malonate esters requires electron-rich and bulky phosphine ligands (Fig. 2, Eq. 1). Aryl iodides and aryl bromides are the substrates of choice and, with some speciality ligands, aryl chlorides can be used as well. The arylated malonate ester is methylated, either in situ or in a separate reaction, hydrolysed under alkaline conditions and decarboxylated under acidic conditions leading to the arylpropionic acid.6 The ester arylation protocol, which is an even more direct route to arylpropionic acids, was developed simultaneously by Hartwig and Buchwald.5 Typically the tert-butyl ester of propionic acid is treated with an aryl halide (bromide or chloride) in the presence of a strong base, palladium and a bulky phosphine ligand or a bulky imidazolinium

Keywords: Palladium catalysis; Enolate arylation; Arylacetic acid esters.

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Figure 1. Examples of nonsteroidal anti-inflammatory drugs.

Figure 2. Synthesis of arylpropionic acids using palladium-catalysed enolate arylation.
biphenyl was also formed in small amounts. The yield of conditions (K₃PO₄, 'Pd(acetate
acylation during the copper-catalysed arylation of aceto-
potassium acetate. McKillop has described a similar de-
ter 2-position, which was then de-acylated under basic tert-
phenylacetate esters resulting in the formation of 2-arylacetic acid esters.

However, with other metals such as copper, the arylation of ethyl acetoacetate with 2-halobenzoic acid was demonstrated in 1929 by Hurtley. The conditions, which consisted of sodium ethoxide in ethanol solution with copper powder or copper(II) acetate, were later refined by McKillop and co-workers. Employing sodium hydride and 6 mol% copper(I) bromide in ethyl acetoacetate solution led to high yields of ethyl β-(2-carboxyphenyl)acetoacetate from ethyl acetoacetate and 2-bromo or chlorobenzoic acid. α-Substituted β-keto esters also reacted under the same conditions although yields were lower. Aryl halides without the ortho-carb-
oxylate group were inactive in these reactions. Aceto-
acetate esters have also been arylated with aryllead triacetates.

In this Letter we wish to disclose novel palladium-catalysed conditions for the arylation of acetoacetate esters resulting in the formation of 2-arylacetic acid esters.

When we attempted the arylation of tert-butyl acetoacetate 1a with bromobenzene 2a using mild reaction conditions (K₃PO₄, ‘Pd(t-Bu₃P)₂', toluene, 90 °C) we did not find any of the desired arylated acetoacetate ester but we identified a substantial amount of tert-butyl phenylacetate 3a (Scheme 1). We assumed that during the tert-butyl acetoacetate was arylated in the 2-position, which was then de-acylated under basic conditions to give the phenylacetate ester 3a and potassium acetate. McKillop has described a similar de-
acylation during the copper-catalysed arylation of acetoacetate with 2-bromobenzoic acid. This reaction was described as a retro-Claisen condensation as sodium ethoxide in ethanol was used, but could also be effected by treating the 2-arylacetoacetate with 2 M NaOH.

Apart from the product tert-butyl phenylacetate 3a, biphenyl was also formed in small amounts. The yield of

Table 1

<table>
<thead>
<tr>
<th>Acetoacetate ester</th>
<th>Catalyst (mol%)</th>
<th>Conv. of 2a (%)</th>
<th>Yield 3 (%)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1% Pd(dba)₂/2% Pd(Bu₃)</td>
<td>67</td>
<td>55</td>
</tr>
<tr>
<td>2b</td>
<td>1% Pd(dba)₂/2% Pd(Bu₃)</td>
<td>100</td>
<td>45</td>
</tr>
<tr>
<td>3b</td>
<td>1% Pd(OAc)₂/2% Pd(Bu₃)</td>
<td>97</td>
<td>48</td>
</tr>
<tr>
<td>4b</td>
<td>5% Pd(OAc)₂/20% PPh₃</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5b</td>
<td>1% Pd(dba)₂/2% PPh₃</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

¹ Yield determined by GC with naphthalene as internal standard.

3a was determined by GC (internal standard) to be 55%. The reaction mixture did not contain any residual acetoacetate ester although a substantial amount of bromobenzene was present. No 2-phenylacetoacetate tert-butyl ester could be detected by GC-MS and 1H NMR spectral analysis.

A similar reaction was observed when ethyl acetoacetate was used under the same conditions (Table 1, entry 2). Ethyl phenylacetate was formed in 45% yield. Reactions were also performed with triphenylphosphine and tricyclohexylphosphine (entries 4 and 5) with no product formation.

Initially, Pd(dba)₂ was used as the catalyst precursor but Pd(OAc)₂ was also found to be as effective (48% yield, Table 1, entry 3).

The use of other aryl halides was investigated. 4-
Bromoanisole 4a resulted in the formation of ethyl (4-
methoxyphenyl)acetate 5a (Scheme 2) albeit in lower yield than ethyl phenylacetate (Table 2, entry 1). 4-
Chloroacetophenone (an activated aryl chloride) also gave the desired arylacetic acid ester 5b but again in lower yield (Table 2, entry 2). The reaction between ethyl acetoacetate and 1-bromonaphthalene gave ethyl (1-naphthyl)acetate 5c albeit in only 15% yield. Hydrodehalogenation of the aryl halide was found to be

Scheme 2. Reagents and conditions: 4 mmol aryl halide, 4.4 mmol acetoacetate ester, 11 mmol K₃PO₄, 5 mL toluene, 0.04 mmol Pd(OAc)₂, 0.08 mmol P(Bu₃)₂BF₄, 90 °C, 16 h (see Table 2 for yields).

Table 2

<table>
<thead>
<tr>
<th>Aryl halide</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>Ethyl (4-methoxyphenyl)acetate 5a</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>Ethyl (4-acetoxy)acetate 5b 30⁶</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>Ethyl (1-naphthyl)acetate 5c 15⁶</td>
</tr>
</tbody>
</table>

⁴ Isolated yield, 35% anisole.
⁶ Isolated yield, 40% acetophenone.
⁵ Isolated yield, 58% naphthalene.
a major side reaction that contributed to aryl halide consumption.

In an effort to improve the yield of the aryl acetate the use of the ligand di-tert-butyl biphenyl phosphine 6 was evaluated (Fig. 3). The use of 6 led to the selective reaction of 2a with 1b to afford ethyl phenylacetate 3b in 56% yield with 95% conversion of bromobenzene (Table 3, entry 1). Full consumption of bromobenzene and a yield of 68% for this reaction was achieved when 2.2 equiv of ethyl acetoacetate (Table 3, entry 2) were used.

This prompted us to test the biphenyl ligand with an extra methyl substituent on the second phenyl ring, that is 7. This ligand has been shown to be especially active in malonate ester arylation.4b Again, this reaction resulted in 89% yield of ethyl phenylacetate when 1 equiv of ethyl acetoacetate was used and 93% with 2 equiv of ethyl acetoacetate (Table 3, entries 3 and 4).

The use of more than 1 equiv of ethyl acetoacetate is thought to lead to improved yields in this reaction; ethyl acetoacetate is the limiting reagent as it is consumed faster than the aryl halide. An increase in ethyl phenylacetate yield was also observed when tri-tert-butylphosphine was used with 2 equiv of ethyl acetoacetate (58% vs 48%, Table 1, entry 3).

Since biphenyl ligands 6 and 7 are known to be active with aryl chlorides in other arylation reactions, chlorobenzene 2b was examined in a reaction employing the standard reaction conditions using ligand 7. Ethyl phenylacetate 3b was produced in 93% yield (by GC, 88% isolated yield, Table 3, entry 5). When the catalyst loading was lowered to 0.2 mol% palladium and 0.4% of 7 a slower reaction was observed. After 16 h at 90 °C, 42% of the chlorobenzene had been consumed while 34% of 3b had been formed. After a total of 70 h the product yield was 49% with a 63% chlorobenzene conversion (Table 3, entry 6). Finally, a reaction was performed with a de-activated aryl chloride. The reaction between 4-chloroanisole 4d and ethyl acetoacetate proceeded smoothly and gave ethyl 4-methoxyphenylacetate 5d (see Scheme 2) in a 75% isolated yield after 40 h at 90 °C, using 0.5% Pd(OAc)2 and 1% of 7 (Table 3, entry 7).

The choice of base has been demonstrated to be essential to the outcome of many arylation reactions.4,5,7,12 The reaction of 1b with 2a to afford ethyl phenylacetate 3b was chosen to investigate this variable. When K2CO3 was used as the base, 20–25% of the anticipated product, ethyl phenylacetate 3b, was formed. In addition, a similar amount of another product, ethyl 2-phenylacetate 8, was identified by spectroscopic techniques. When sodium tert-butoxide was used as the base, the starting materials were consumed and only a small amount of product 3b was formed.

Subsequently, an investigation of our standard transformation (1b + 2a → 3b) by varying the concentration of K3PO4 was conducted. The same by-product 8 was detected in all reactions but to a much smaller extent than with the other bases. In a typical reaction, with the molar ratio of K3PO4 to ethyl acetoacetate being 2:4:1, the amount of side-product 8 (Fig. 4) was between 1% and 5%. When the base to substrate ratio was changed to 2:1, between 10% and 15% of 8 was detected, while the ethyl phenylacetate yield dropped by a similar amount. This effect was further demonstrated by lowering the base concentration to 0.6 equiv K3PO4 in relation to ethyl acetoacetate. Only 15% of the desired product 3b was formed and 55% of 8 was produced. From this observation it was clear that ethyl acetoacetate is arylated in the 2-position during the reaction. The formation of ethyl phenylacetate then occurs when this intermediate undergoes base mediated cleavage. This second step is clearly dependant on base concentration and strength. To demonstrate this, separate reactions were run with a lower concentration of K3PO4 to form 8, followed by addition of extra K3PO4 and further heating. It was noticed that the intermediate 8 was depleted entirely after heating for 5 h with an increase in ethyl phenylacetate 3b yield equal to the intermediate 8 consumed.

![Figure 3](image-url)

![Figure 4](image-url)

Table 3

<table>
<thead>
<tr>
<th>Aryl halide</th>
<th>Catalyst (mol%)</th>
<th>Conv. of PhBr (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a 1% Pd(OAc)2/2% 6</td>
<td>95</td>
<td>56a</td>
</tr>
<tr>
<td>2</td>
<td>2a 2% Pd(OAc)2/4% 6</td>
<td>100</td>
<td>68b</td>
</tr>
<tr>
<td>3</td>
<td>2a 1% Pd(OAc)2/2% 7</td>
<td>100</td>
<td>89a</td>
</tr>
<tr>
<td>4</td>
<td>2a 2% Pd(OAc)2/4% 7</td>
<td>100</td>
<td>93b</td>
</tr>
<tr>
<td>5</td>
<td>2b 2% Pd(OAc)2/4% 7</td>
<td>100</td>
<td>93b</td>
</tr>
<tr>
<td>6</td>
<td>2b 0.2% Pd(OAc)2/0.4% 7</td>
<td>63</td>
<td>49b</td>
</tr>
<tr>
<td>7</td>
<td>4d 0.5% Pd(OAc)2/1% 7</td>
<td>100</td>
<td>75b,c</td>
</tr>
</tbody>
</table>

*aConditions: 4 mmol bromobenzene, 4.4 mmol acetoacetate ester, 11 mmol K3PO4, 5 mL toluene, 90 °C, 16 h.
*bConditions: 2 mmol bromobenzene, 4.4 mmol acetoacetate ester, 11 mmol K3PO4, 5 mL toluene, 90 °C, 16 h.
*cIsolated yield.
It seems that not only the strength of the base but also its availability must be tempered to match the rate of enolate formation with the rate of the arylation reaction. The same observation has been made by Buchwald in the amidation of aryl halides. Both K$_3$PO$_4$ and K$_2$CO$_3$ are thought to be thermodynamically strong bases in aprotic solvents but their low solubility in toluene ensures a slow formation of enolate. From the fact that no arylation of ethyl phenylacetate was observed using K$_3$PO$_4$ as the base while the use of sodium tert-butoxide under identical reaction conditions, did yield ethyl diphenylacetate (58%), it is concluded that K$_3$PO$_4$ is not strong enough to deprotonate a phenyl acetate ester.

In conclusion, this work constitutes the first example of a palladium-catalysed intermolecular arylation of an acetoacetate ester. We have demonstrated the formation of the arylated acetoacetate ester (e.g., 8) and its in situ base catalysed de-acylation to an arylacetate ester (e.g., 3b). A variety of mono-arylated acetate esters can be prepared in this manner and the reaction is applicable to both aryl bromides and chlorides.

References and notes