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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 K_3PO_4 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-arylacetic or arylpropionic acids. For example, the preparation of ibuprofen by way of arylation of methylmalonic acid esters using an aryllead triacetate 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]

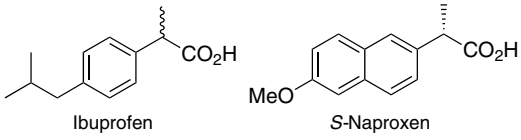

Figure 1. Examples of nonsteroidal anti-inflammatory drugs.

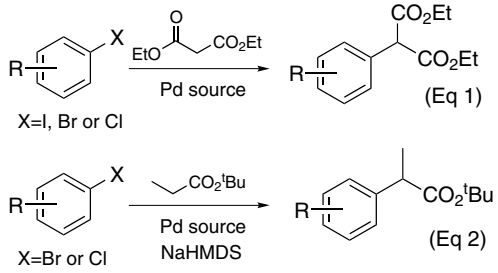

Figure 2. Synthesis of arylpropionic acids using palladium-catalysed enolate arylation.

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

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carbene (Fig. 2, Eq. 2). A disadvantage of this procedure is that very specific bases have to be used, sodium hexamethyldisilazane (NaHMDS) (for propionate esters) and LiHMDS (for acetate esters). These bases are also expensive and moisture sensitive.

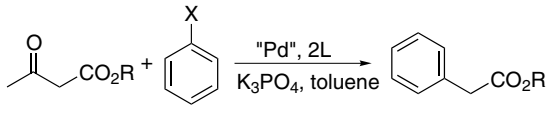
Although a large number of enolates have been utilised in palladium-catalysed arylation chemistry,[7] acetoacetate esters and acetylacetones, have not yet been successfully arylated. The explanation presented for the lack of success with these substrates is linked to the ability of the enolates of these compounds to form stable complexes with metals.[4a,d]

However, with other metals such as copper, the arylation of ethyl acetoacetate with 2-halobenzoic acid was demonstrated in 1929 by Hurtley.[8] 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.[9] 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*-carboxylate group were inactive in these reactions. Acetoacetate esters have also been arylated with aryllead triacetates.[10]

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 (K_3PO_4, '$Pd(t\text{-}Bu_3P)_2$', 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 reaction *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.[9] 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.[11]

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



Scheme 1. Reagents and conditions: 4 mmol bromobenzene, 4.4 mmol acetoacetate ester, 11 mmol K_3PO_4, 5 mL toluene, 0.04 $Pd(dba)_2$ or $Pd(OAc)_2$, 0.08 mmol ligand, 90 °C, 16 h (see Table 1 for catalyst and ligand, percentage conversion of **2** and yields).

Table 1

	Acetoacetate ester	Catalyst (mol%)	Conv. of **2a** (%)	Yield **3** (%)[a]
1	**1a**	1% $Pd(dba)_2$/2% P^tBu_3	67	55
2	**1b**	1% $Pd(dba)_2$/2% P^tBu_3	100	45
3	**1b**	1% $Pd(OAc)_2$/2% P^tBu_3	97	48
4	**1b**	5% $Pd(OAc)_2$/20% PPh_3	0	0
5	**1b**	1% $Pd(dba)_2$/2% PCy_3	0	0

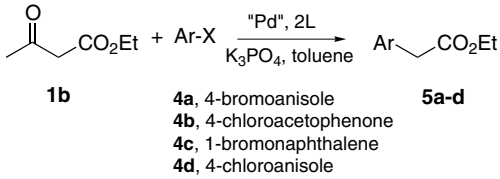
[a] Yield determined by GC with naphthalene as internal standard.

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 K_3PO_4, 5 mL toluene, 0.04 mmol $Pd(OAc)_2$, 0.08 mmol $P^tBu_3{\cdot}HBF_4$, 90 °C, 16 h (see Table 2 for yields).

Table 2

	Aryl halide	Product	Yield (%)
1	**4a**	Ethyl (4-methoxyphenyl)acetate **5a**	40[a]
2	**4b**	Ethyl (4-acetophenyl)acetate **5b**	30[b]
3	**4c**	Ethyl (1-naphthyl)acetate **5c**	15[c]

[a] Isolated yield, 35% anisole.
[b] Isolated yield, 40% acetophenone.
[c] Isolated yield, 58% naphthalene.

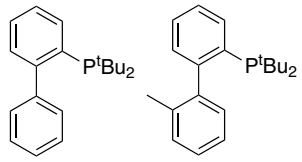


Figure 3.

a major side reaction that contributed to aryl halide consumption.

In an effort to improve the yield of the arylacetate the use of the ligand di-*tert*-butyl biphenyl phosphine **6**[4b] 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).

Table 3

	Aryl halide	Catalyst (mol%)	Conv. of PhBr (%)	Yield (%)
1	**2a**	1% $Pd(OAc)_2$/2% **6**	95	56[a]
2	**2a**	2% $Pd(OAc)_2$/4% **6**	100	68[b]
3	**2a**	1% $Pd(OAc)_2$/2% **7**	100	89[a]
4	**2a**	2% $Pd(OAc)_2$/4% **7**	100	93[b]
5	**2b**	2% $Pd(OAc)_2$/4% **7**	100	93[b]
6	**2b**	0.2% $Pd(OAc)_2$/0.4% **7**	63	49[b]
7	**4d**	0.5% $Pd(OAc)_2$/1% **7**	100	75[b,c]

[a] Conditions: 4 mmol bromobenzene, 4.4 mmol acetoacetate ester, 11 mmol K_3PO_4, 5 mL toluene, 90 °C, 16 h.
[b] Conditions: 2 mmol bromobenzene, 4.4 mmol acetoacetate ester, 11 mmol K_3PO_4, 5 mL toluene, 90 °C, 16 h.
[c] Isolated yield.

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 K_2CO_3 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-phenylacetoacetate **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 K_3PO_4 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 K_3PO_4 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 K_3PO_4 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 K_3PO_4 to form **8**, followed by addition of extra K_3PO_4 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.

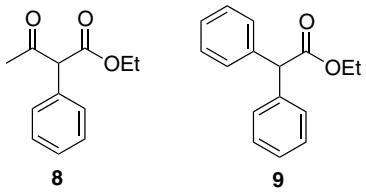


Figure 4.

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.[12c] Both K_3PO_4 and K_2CO_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_3PO_4 as the base while the use of sodium *tert*-butoxide under identical reaction conditions, did yield ethyl diphenylacetate **9** (58%), it is concluded that K_3PO_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.

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