

## Copper(I) iodide-catalysed arylation of acetoacetate to yield 2-arylacetic acid esters

Jacob G. Zeevaart,<sup>a</sup> Christopher J. Parkinson<sup>a,\*</sup> and Charles B. de Koning<sup>b</sup>

<sup>a</sup>Discovery Chemistry, CSIR, Biosciences, Modderfontein 1645, South Africa

<sup>b</sup>Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, WITS 2050, South Africa

Received 29 January 2007; revised 19 February 2007; accepted 28 February 2007

Available online 4 March 2007

**Abstract**—The C–C coupling reaction between ethyl acetoacetate and aryl halides in the presence of CuI is described. The effects of solvent, ligands such as vicinal diamines and amino acids, base and temperature are reported. The arylated acetoacetate ester is deacylated under the reaction conditions resulting in the generation of 2-arylacetic acid esters, constituting a mild alternative to direct arylation of carboxylate esters.

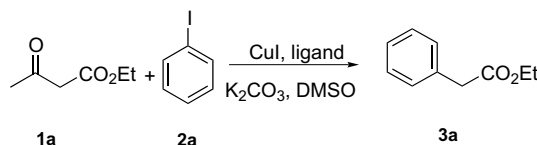
© 2007 Elsevier Ltd. All rights reserved.

The preparation of 2-arylalkanoic acid derivatives, especially arylpropionic acids has received significant attention during the past few years since they find application as non-steroidal anti-inflammatory drugs (NSAID).<sup>1</sup> Direct arylation of acetic acid esters has recently been demonstrated but suffers from the high reactivity of the ester enolate.<sup>2</sup> The arylation of easily accessible  $\beta$ -diester carbanions have been investigated as a milder alternative strategy to obtain 2-arylacetic or arylpropionic acids via decarboxylation.<sup>3–5</sup>

We recently reported on the palladium catalysed arylation of ethyl acetoacetate to yield ethyl esters of 2-arylacetic acid by in situ deacetylation of the 2-arylated acetoacetate intermediate promoted by temperature and excess base.<sup>6</sup> At the conclusion of that investigation, we set out to examine the use of cheaper transition metals and to offset the reliance of the reaction on air sensitive or expensive ligands. We now report on the use of catalytic CuI for the same purpose. Copper-catalysed arylation of ethyl cyanoacetate and diethyl malonate has been demonstrated using aryl iodides by various groups.<sup>3</sup> A recent paper described the arylation of ethyl acetoacetate employing CuI/L-proline and various aryl iodides as well as some examples of aryl bromides.<sup>7</sup>

The products were the 2-arylated acetoacetates while no mention was made about the deacetylated product—the  $\alpha$ -aryl ester.

We investigated the copper-catalysed reaction between ethyl acetoacetate and iodobenzene in a number of solvents with varying polarity and donor properties (see Scheme 1). The results in Table 1 indicate that the reaction performs better in more polar solvents, optimum results being observed in dimethyl sulfoxide (DMSO), particularly when an additional ligand was not employed in the reaction. Although the reaction did proceed in 1,4-dioxane, the rate of reaction was much lower and **3a** was produced in low yield (entry 3). *N,N'*-Dimethylformamide (DMF) and *N*-methylpyrrolidinone (NMP) also proved to be effective solvents. Toluene, the solvent of choice for our previous palladium/phosphine catalysed reactions,<sup>6</sup> was not suitable for the CuI catalysed reaction in the absence of additional



**Scheme 1.** Reagents and conditions: 2 mmol Iodobenzene, 4 mmol ethyl acetoacetate, 8 mmol  $\text{K}_2\text{CO}_3$ , 0.4 mmol CuI, 0.8 mmol ligand, 5 ml solvent, 80 °C, 20 h (see Table 1 for type of ligand used, conversions and yields).

**Keywords:** Ethyl acetoacetate; Arylacetic acid esters; CuI; Enolate arylation; Aryl iodide.

\*Corresponding author. Tel.: +27 116052601; fax: +27 116083200; e-mail: cparkinson@csir.co.za

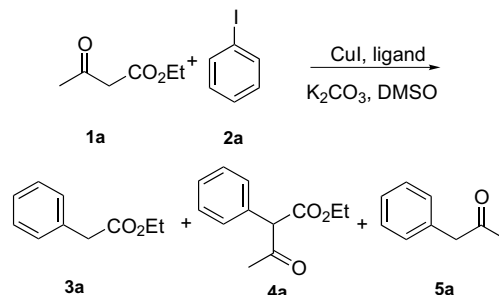
Table 1.

	Ligand	Solvent	Conv. of <b>1a</b>	Conv. of <b>2a</b>	Yield of <b>3a</b>
1	None	DMSO	100	52	53
2	None	DMSO <sup>a</sup>	63	75	56
3	None	Dioxane	62	20	12
4	None	NMP	91	nd	42
5	None	DMF	89	42	43
6	Ethylenediamine	DMSO	100	86	29
7	Ethylenediamine	Dioxane	84	64	48
8	Ethylenediamine	Toluene	80	45	38
9	<i>N,N'</i> -Dimethyl ethylenediamine	Dioxane	87	34	26
10	<i>N,N'</i> -Dimethyl ethylenediamine	Toluene	61	50	23
11	2-Phenylphenol	DMSO	93	70	41
12	2-Phenylphenol	Dioxane	67	5	5

<sup>a</sup> CuBr used.

ligand. The fact that the more polar solvents play an important role in stabilising the catalyst or transition state, something which was restricted in the case of dioxane and absent in the case of toluene, was demonstrated by achieving much improved yields in these two solvents by adding ethylenediamine as a ligand (entries 7 and 8). The addition of ethylenediamine to the reaction in DMSO, however, had a detrimental effect (entry 6). The use of *N,N'*-dimethylated ethylenediamine showed a similar effect but to a lesser extent. Aliphatic vicinal diamines have been shown to be useful in copper-catalysed amidation and amination of aryl halides (Goldberg and Ullmann reactions).<sup>8</sup> The use of 2-phenylphenol, which has been used by Buchwald in the copper-catalysed arylation of malonates,<sup>3c</sup> exhibited a marginal retardation effect in DMSO but deactivated the dioxane system almost completely (entries 11 and 12).

In order to improve the efficacy of the CuI catalysed reaction, the more traditional bidentate diamine ligands used in Ullmann-type couplings<sup>9</sup> were investigated (Table 2). It was noted that in many reactions the conversion of iodobenzene exceeded the yield of **3a**. Initially, it was thought that hydrodehalogenation or homocoupling to biphenyl must be responsible for the excessive consumption of iodobenzene but it was later found that significant amounts of the initial arylation product, ethyl 2-phenylacetoacetate **4a**, remained in the reaction mixture. Small amounts of phenylacetone **5a** were also de-



**Scheme 2.** Reagents and conditions: 2 mmol Iodobenzene, 4 mmol ethyl acetoacetate, 8 mmol K<sub>2</sub>CO<sub>3</sub>, 0.4 mmol CuI, 0.8 mmol ligand, 5 ml solvent, 80 °C, 20 h (see Table 2 for type of ligand used, conversions and yields).

tected, presumably via hydrolysis and decarboxylation of **4a** (see Scheme 2).

The use of 1,1'-bipyridine, 1,10-phenanthroline or 1,8-diaminonaphthalene in conjunction with CuI did not significantly influence formation of the required product **3a**. The significantly higher conversion of iodobenzene in the reaction with 1,8-diaminonaphthalene is believed to be due to competing *N*-arylation of the primary amine groups of the ligand. The recent surge of publications on the use of amino acids as ligands for copper,<sup>10</sup> prompted us to investigate a range of amino acids in this reaction (entries 5–10). Once again no improvements were detected in DMSO, demonstrating that DMSO acts as a sufficient ligand for copper in this reaction. Conversion of iodobenzene again was high in comparison with the arylated products formed especially for amino acids with primary amines. This effect was, however, not evident in the reactions performed in dioxane, reactions in this solvent proving more selective.

We next investigated the effect of temperature and the type and amount of base on the relative yields of **3a** and **4a** (Table 3). At a lower reaction temperature (40 °C), the reaction was slower and resulted in a much higher yield of **4a**. The combined yield of **3a** and **4a** was, however, approximately the same as that recorded at 80 °C. This indicates that the deacylation reaction of **4** to **3** is promoted by higher temperature. The much higher selectivity with ethyl acetoacetate (52%, entry 1) at 40 °C confirms this trend, typically only 30–40% of consumed ethyl acetoacetate is utilised in the arylation reac-

Table 2.

	Ligand	Solvent	Conv. of <b>1a</b>	Conv. of <b>2a</b>	Yield of <b>3a</b>	Yield of <b>4a</b>
1	None	DMSO	92	74	54	18
2	1,1'-Bipyridine	DMSO	94	76	54	20
3	1,10-Phenanthroline	DMSO	96	75	41	17
4	1,8-Diaminonaphthalene	DMSO	86	88	47	22
5	Proline	DMSO	89	79	45	8
6	Phenylalanine	DMSO	100	100	48	6
7	Phenylalanine	Dioxane	66	53	42	8
8	Tryptophan	DMSO	99	99	37	11
9	Ornithine	DMSO	99	79	17	7
10	2,4-Diaminobutyric acid	Dioxane	61	21	18	6

Table 3.

	Temperature (°C)	Base (equiv)	Conv. of <b>1a</b>	Conv. of <b>2a</b>	Yield of <b>3a</b>	Yield of <b>4a</b>
1	40 <sup>a</sup>	K <sub>2</sub> CO <sub>3</sub> (4)	73	85	38	38
2	80	K <sub>2</sub> CO <sub>3</sub> (4)	92	74	54	18
3	80 <sup>b</sup>	K <sub>2</sub> CO <sub>3</sub> (1)	63	48	16	34
4	80	K <sub>2</sub> CO <sub>3</sub> (2)	95	71	53	16
5	80 <sup>c</sup>	K <sub>2</sub> CO <sub>3</sub> (7.5)	100	98	86	4
6	80	Cs <sub>2</sub> CO <sub>3</sub> (4)	60	50	7	17
7	80	K <sub>3</sub> PO <sub>4</sub> (1)	89	52	20	26

Reagents and conditions: 2 mmol Iodobenzene, 4 mmol ethyl acetoacetate, 2–15 mmol base, 0.4 mmol CuI, 0.8 mmol ligand, 5 ml solvent, 40/80 °C, 20 h.

<sup>a</sup> Reaction time: 40 h.

<sup>b</sup> Reaction time: 7 h.

<sup>c</sup> 10 mmol **1a** used.

tion while the rest is consumed by deacylation to form ethyl acetate and potassium acetate.

Unlike recently reported results<sup>3e,7</sup> suggesting the superior behaviour of Cs<sub>2</sub>CO<sub>3</sub> as base, we were not able to obtain satisfactory results with this base and concluded that for this particular reaction, K<sub>2</sub>CO<sub>3</sub> is the preferred base. Although much lower yields were obtained with Cs<sub>2</sub>CO<sub>3</sub>, it did appear to favour the arylated acetoacetate **4a** and was much less effective in the deacylation reaction to ethyl phenylacetate **3a**. This suggests that the arylation reaction is inhibited by the build-up of arylated acetoacetate and is, in fact, promoted by the in situ deacylation of the product. Ethyl phenylacetoacetate **4a** is likely to be fully deprotonated under the reaction conditions, due to its enhanced thermodynamic acidity, and hence may deactivate the copper catalyst by the formation of a stable chelate.

The use of potassium phosphate resulted in high conversion of the starting material but lower product yields. This may be attributable to the increased levels of deacylation of the substrate ethyl acetoacetate, resulting in a deficiency of the required nucleophile. By decreasing the amount of K<sub>3</sub>PO<sub>4</sub> to 1 M equiv to iodobenzene, a moderate yield of **3a** and **4a** was achieved. The higher deacylation reactivity of K<sub>3</sub>PO<sub>4</sub> in DMSO compared to in toluene (as used in the palladium catalysed reactions<sup>6</sup>),

is ascribed to the relatively insoluble nature of K<sub>3</sub>PO<sub>4</sub> in toluene which tempers the action of the base in that solvent. For the purposes of effecting the required transformation, K<sub>2</sub>CO<sub>3</sub> should be considered the preferred base.

The number of stoichiometric equivalents of K<sub>2</sub>CO<sub>3</sub> used in the reaction also determined the relative amounts of **3a** and **4a**. Higher base loading promoted the formation of **3a**. When the amount of base was limited to only 1 equiv relative to iodobenzene, the effect of the base becomes visible as **4a** becomes the predominant product (Table 3, entry 3). When a large quantity of base was used (such as in entry 5, Table 3), relatively small amounts of **4a** were isolated. Apart from the higher ratio of base to product which promotes deacylation, the higher reaction rate leads to the formation of more product (**4a**) early in the reaction profile which is, therefore, exposed to deacylation conditions for longer periods of time. The high yield of **3a** when using several stoichiometric equivalents of ethyl acetoacetate (Table 3, entry 5, 5 M equiv) and 7.5 equiv of base relative to iodobenzene prompted us to further investigate these conditions.

A number of reactions with 5 equiv of ethyl acetoacetate were performed under slightly different conditions (Table 4). The reactions in DMSO at 80 °C gave **3a** as the major product in good yield, even at lower CuI loading (Table 4, entries 2 and 3), while **4a** was the dominant product when the reaction was carried out at 40 °C. The reaction at 40 °C was remarkably selective in the conversion of ethyl acetoacetate when compared to the reactions performed at 80 °C (combined yield of **3a** and **4a** based on **1a** conversion of 72% at 40 °C compared to 18% at 80 °C, Table 4, entries 4 and 1). This presents an avenue to improve the utilisation of ethyl acetoacetate. The reaction in dioxane when using ethylenediamine as ligand also provided **3a** in relatively good yield with higher selectivity in the utilisation of ethyl acetoacetate (Table 4, entry 6).

The applicability of the optimised reaction conditions (as demonstrated in Table 4) to other aryl iodides was demonstrated and the effects of substituents on product distribution were evaluated (see Scheme 3 and Table 5).

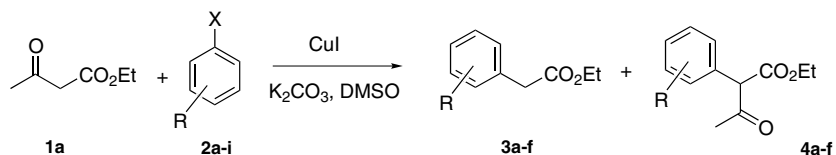
Table 4.

	Ligand	Solvent	Temperature (°C)/Time (h)	Base (equiv)	Conv. of <b>1a</b>	Conv. of <b>2a</b>	Yield of <b>3a</b>	Yield of <b>4a</b>
1	None	DMSO	80 (20 h)	K <sub>2</sub> CO <sub>3</sub> (7.5)	100	98	86	4
2	None <sup>a</sup>	DMSO	80 (20 h)	K <sub>2</sub> CO <sub>3</sub> (7.5)	80	97	85	9
3	None <sup>b</sup>	DMSO	80 (24 h)	K <sub>2</sub> CO <sub>3</sub> (5)	85	96	85	11
4	None	DMSO	40 (20 h)	K <sub>2</sub> CO <sub>3</sub> (7.5)	26	81	17	65
			40 (40 h)		26	92	37	56
5	None	Dioxane	80 (44 h)	K <sub>2</sub> CO <sub>3</sub> (7.5)	69	83	58	7
6	Ethylene diamine	Dioxane	80 (40 h)	K <sub>2</sub> CO <sub>3</sub> (7.5)	63	87	72	3
7	Ethylene diamine	Toluene	80 (44 h)	K <sub>3</sub> PO <sub>4</sub> (5)	49	15	15	0

Reagents and conditions: 2 mmol Iodobenzene, 10 mmol ethyl acetoacetate, 10–15 mmol base, 0.4 mmol CuI, 0.8 mmol ligand, 8 ml solvent, 40/80 °C, 20–44 h.

<sup>a</sup> 10 mol % CuI used.

<sup>b</sup> 5 mol % CuI used.



**Scheme 3.** Reagents and conditions: 2 mmol Aryl halide **2**, 10 mmol ethyl acetoacetate, 15 mmol  $\text{K}_2\text{CO}_3$ , 0.4 mmol  $\text{CuI}$ , 8 ml DMSO, 80 °C, 20 h (see Table 5 for conversions and yields).

4-Iodoanisole **2b** behaved very similarly to iodobenzene and gave the desired 2-arylacetic acid ester in high yield. A much lower yield was, however, obtained when using 2-iodotoluene and the arylated acetoacetate **4c** was the major product possibly due to steric effects which both limited the arylation and deacylation reaction. The use of electron deficient aryl iodides gave fast reactions with high combined yields of **3** and **4**. Unlike iodobenzene and 4-iodoanisole, a much higher proportion of the arylated acetoacetate remained in the product mixture. The higher acidity of these products (**4d** and **4e**) could reduce

the electrophilicity of the carbonyl which must be attacked prior to decarbonylation.

Several aryl bromides were also tested under similar conditions, non-activated aryl bromides showed only traces of products (entries 6 and 7) while the use of activated aryl bromides was more successful (entries 8 and 9). Although the reaction involving 4-bromobenzonitrile **2i** was sluggish and yields of **3f** and **4f** were relatively low, the use of 4-bromoacetophenone **2h** resulted in a facile reaction with a good combined yield of **3d** and

**Table 5.**

	Ar-X	Conversion Ar-X (%)	Conversion acetoacetate (%)	Products (yield)	
1	<b>2a</b>	100	77	<b>3a</b> 89%	<b>4a</b> 9%
2	<b>2b</b>	100	78	<b>3b</b> 93%	<b>4b</b> 7%
3	<b>2c</b>	93	90	<b>3c</b> 19%	<b>4c</b> 41%
4	<b>2d</b>	100	76	<b>3d</b> 63%	<b>4d</b> 35%
5	<b>2e</b>	100	80	<b>3e</b> 53%	<b>4e</b> 41%
6	<b>2f</b>	13	n.d	<b>3a</b> 2%	
7	<b>2g</b>	0 <sup>a</sup>	88	No arylation products detected	
8	<b>2h</b>	76	80	<b>3d</b> 48%	<b>4d</b> 22%
9	<b>2i</b>	43 <sup>a</sup>	94	<b>3f</b> 6%	<b>4f</b> 13%

**4d** although inferior to the result achieved with the corresponding iodo substrate. Further work is required before a general procedure for utilising aryl bromides can be proposed.

In conclusion, we have demonstrated the formation of ethyl esters of 2-arylacetic acids from ethyl acetoacetate and aryl iodides (as well as electron-deficient aryl bromides) in high yield by using copper(I) catalysis in the absence of additional ligands.<sup>11</sup> At lower temperature, the reaction is more selective in the conversion of ethyl acetoacetate but results in a higher yield of the arylated acetoacetate. Prolonged heating shifts the product distribution towards the 2-arylacetic acid esters. Although DMSO is the preferred solvent for this reaction, moderate to good results were also possible in 1,4-dioxane with the addition of ethylenediamine as ligand.

### References and notes

1. Lednicer, D.; Mitscher, L. A. In *The Organic Chemistry of Drug Synthesis*; John Wiley: New York, 1980; Vol. 2, p 62.
2. (a) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996; (b) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410; (c) Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557; (d) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176.
3. (a) Setsune, J.-I.; Matsukawa, K.; Wakemoto, H.; Kitao, T. *Chem. Lett.* **1981**, 367; (b) Osuka, A.; Kobayashi, T.; Suzuki, H. *Synthesis* **1983**, 67; (c) Ugo, R.; Nardi, P.; Rinaldo, P.; Roberto, D. *Gazz. Chim. Ital.* **1992**, *122*, 511; (d) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606; (e) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269.
4. Pinhey, J. T.; Rowe, B. A. *Tetrahedron Lett.* **1980**, *21*, 965.
5. (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473; (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360; (c) Kondo, Y.; Inamoto, K.; Uchiyama, M.; Sakamoto, T. *Chem. Commun.* **2001**, 2704; (d) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.
6. Zeevaart, J. G.; Parkinson, C. J.; de Koning, C. B. *Tetrahedron Lett.* **2004**, *45*, 4261.
7. Xie, X.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 4693.
8. (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421; (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *123*, 7727.
9. (a) Beletskaya, I. P.; Cheprakov, A. V. *Coordin. Chem. Rev.* **2004**, *248*, 2337; (b) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657; (c) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315.
10. (a) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453; (b) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799; (c) Deng, W.; Wang, Y.; Zou, W.; Liu, L.; Guo, Q. *Tetrahedron Lett.* **2004**, *45*, 2311; (d) Deng, W.; Zou, Y.; Wang, Y. F.; Liu, F.; Guo, Q. X. *Synlett* **2004**, 1254; (e) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164; (f) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809; (g) Ma, D.; Cai, Q. *Synlett* **2004**, *1*, 128.
11. Typical experimental procedure for the CuI-catalysed reaction between ethyl acetoacetate and an aryl halide: A screw capped Pyrex tube (50 ml) was charged with powdered potassium carbonate (2.1 g, 15 mmol), dry solvent (8 ml), ethyl acetoacetate (1.3 g, 10 mmol) and aryl halide (2 mmol). CuI (20–80 mg, 0.1–0.4 mmol, 5–20 mol%) and naphthalene (internal standard) were added. The tube was flushed with nitrogen, sealed and heated to 80 °C for 20 h. The amounts of ethyl acetoacetate, aryl halide and ethyl 2-arylacacetate in the reaction mixture were determined by GC analysis based on internal standard calculation. Isolation was performed by dilution with ethyl acetate (20 ml), water (10 ml) and acidification with dilute hydrochloric acid (10% m/V). The organic layer was diluted with hexane (40 ml) and washed with brine (3 × 20 ml) before drying over anhydrous MgSO<sub>4</sub> and concentration in vacuo. Column chromatography was performed on silica gel eluting with 5–10% ethyl acetate in hexane.