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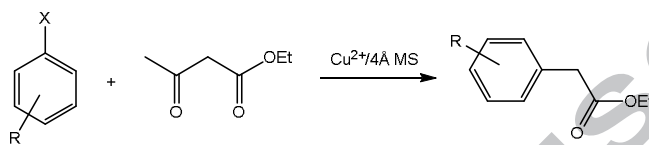


Graphical Abstract

Selective synthesis of arylacetic acid esters from ethyl acetoacetate and aryl halides in the presence of copper(II) on 4Å molecular sieves

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Selective synthesis of arylacetic acid esters from ethyl acetoacetate and aryl halides in the presence of copper(II) on 4Å molecular sieves

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ABSTRACT

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A heterogeneous catalyst, copper(II) on 4Å molecular sieves has successfully been used in the arylation of ethyl acetoacetate, selectively forming arylacetic esters in high yields. The air stable and easily handled catalyst can be simply filtered off during purification thus avoiding significant metal contamination of the product.

Keywords:

Arylacetic esters
Copper
Heterogeneous catalysis
4Å molecular sieves
Selective synthesis

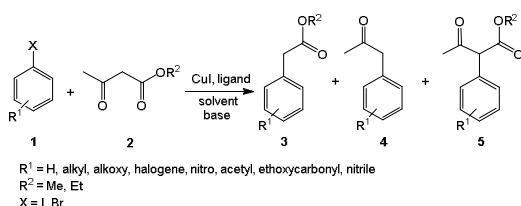
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Introduction

Arylacetic esters are valuable intermediates in the synthesis of several active pharmaceutical ingredients, which for example include non-steroidal anti-inflammatory drugs, such as Ibuprofen or Naproxen.¹ Several homogeneous catalytic methods have been reported for their preparation, using copper(I)-halides that have been modified with an organic ligand, in the presence of base (e.g. K_2CO_3).²⁻⁵ The main disadvantage of these methods is the separation of the catalyst and ligand from the product, which is especially relevant when the high purity requirements of the pharmaceutical and fine chemical industries are taken into consideration. Moreover these homogeneous reactions are often unselective, and require long reaction times (e.g. 48 h⁴) (Figure 1). Therefore, the development of new heterogeneous catalytic methods for the arylation of CH-acids still may have synthetic importance.

Figure 1: General scheme for the copper catalysed coupling of aryl halides with acetoacetic esters



Previously, our research group has reported a copper(II) catalyst supported on 4Å molecular sieves ($Cu^{2+}/4\text{\AA} MS$) which has been successfully used in several heterogeneous catalytic reactions, including alkyne-amine-aldehyde coupling⁶ or the coupling of boronic acids with amines.⁷

Results and discussion

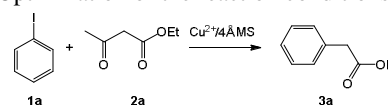
Initially, we investigated the applicability of this catalyst to the ligand free arylation of CH-acids using iodobenzene (**1a**) and ethyl acetoacetate (**2a**). In the presence of K_2CO_3 in boiling xylene, ethyl phenylacetate (**3a**) was obtained as the sole product (Table 1, entry 5). The catalyst could be removed by simple filtration and no significant copper contamination of the product was detected by X-ray fluorescence (XRF). Without extractive workup the measured copper content was approximately 3 ppm and this could be easily removed by washing the product with water.

To the best of our knowledge, there is only one other example describing such a selective reaction.⁸ In this example a homogeneous palladium catalyst was used in combination with a bulky and electron rich phosphine.

The optimal reaction conditions were determined using the model reaction of iodobenzene and ethyl acetoacetate. Since it was previously reported² that use of excess base improved the selectivity towards the desired phenylacetic ester derivatives, 2.5 equiv. of base was utilised. The results are summarised in Table 1. It was found that the reaction required a strong base. The use of Na_2CO_3 was inefficient, and the starting materials were recovered from the reaction mixture (entries 1-3), while in the presence of K_2CO_3 , a significant amount of product was only obtained in boiling xylene (entry 5). Use of Cs_2CO_3 gave better results (entries 11, 12, 14-16). The best yield was obtained using dioxane as solvent. Surprisingly, in DMF and DMSO, which are commonly used solvents in homogeneous catalytic methods,^{2,4,5} no product was obtained (entries 6 and 10). Increasing the excess

of ethyl acetoacetate from 0.2 to 0.5 equiv. also resulted in an increase in yield (entry 16). GC-MS analysis of the reaction mixture showed that after 12 h there was no significant increase in conversion (Figure 2).

Table 1: Optimization of the reaction conditions^a



Entry	Base	Solvent	Temperature (°C)	Yield (%) ^b
1	Na_2CO_3	xylene	145	0
2	Na_2CO_3	acetonitrile	80	0
3	Na_2CO_3	dioxane	100	0
4	K_2CO_3	dioxane	100	<5
5	K_2CO_3	xylene	145	62
6	K_2CO_3	DMF	150	0
7	K_2CO_3	toluene	110	2
8	K_2CO_3	THF	66	0
9	K_2CO_3	ethanol	80	2
10	K_2CO_3	DMSO	80	0
11 ^c	Cs_2CO_3	xylene	145	64
12 ^c	Cs_2CO_3	toluene	110	58
13	Cs_2CO_3	acetonitrile	80	0
14	Cs_2CO_3	xylene	145	30
15	Cs_2CO_3	dioxane	100	80
16 ^d	Cs_2CO_3	dioxane	100	90

^aIodobenzene (5 mmol), ethyl acetoacetate (6 mmol), $Cu^{2+}/4\text{\AA} MS$ (0.5 g, 0.1 mol% copper), base (12.5 mmol), solvent (10 ml), reflux, 24 h

^bBased on the GC-MS analysis of the product

^c5 mmol base

^d7.5 mmol ethyl acetoacetate

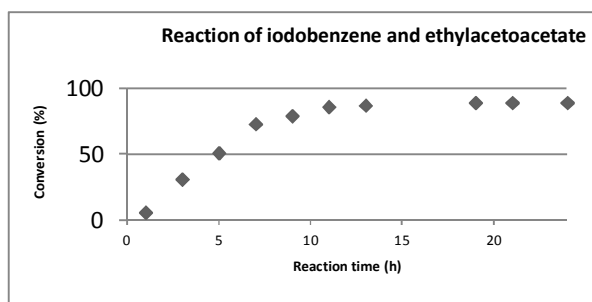


Figure 2

We then examined the reaction using different aryl halides (Table 2). Aryl iodides gave generally high yields (entries 1-5), except in the cases where the aryl halide contained a hydrolysable substituent, and, either no product was obtained (entries 7,8) or the yield was very poor (entry 11). This can be explained by the thermal acid-base disproportionation of bicarbonates into carbonates and carbonic acid. The decomposition of the latter provides water which, in the strong basic media, hydrolyses the ester functional group of the acetoacetate and/or the aryl halides. The acid caesium salt obtained either fails to react or the products were lost during workup of the reaction mixture. In case of entries 7 and 8 the steric hindrance of the *ortho*-substituents combined with this hydrolytic effect could block the formation of the desired products completely. The hydrolytic side reaction can be proved with the high yield obtained in the reaction of an amide (entry

12) which cannot be easily hydrolysed under the reaction conditions used. In a related homogenous catalytic process a reduction in the yield was also been observed² in the case of aryl iodides containing hydrolysable functions (but it was only described without any discussion).

The strong steric effect was also confirmed by the poor yield obtained in the reaction of 2-phenoxy-iodobenzene (entry 9). Aryl bromides were unreactive, and even after extended reaction times could be almost completely recovered from the reaction mixture (entries 13-16).

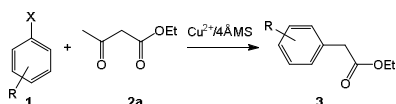


Figure 3

Table 2: Reaction of ethyl acetoacetate with aryl halides^a

Entry	R	X	Product	Yield (%) ^b
1	H	I	3a	83
2	3-NO ₂	I	3b	86
3	4-NO ₂	I	3c	85
4	3-CH ₃	I	3d	75
5	4-CH ₃	I	3e	84
6	4-CH ₃ O	I	3f	33
7	2-CH ₃ COO	I	3g	0
8	2-COOEt	I	3h	0
9	2-C ₆ H ₅ O	I	3i	14
10	4-Br	I	3j	50
11	4-COOEt	I	3k	26
12	4-CONH <i>i</i> Pr	I	3l	89
13	H	Br	3a	0
14	4-CH ₃	Br	3e	0
15	4-CH ₃ O	Br	3f	0
16	3-CH ₃	Br	3d	0

^aAryl halide (5 mmol), ethyl acetoacetate (7.5 mmol), Cu²⁺/4Å MS (0.5 g, 0.1 mol% copper), Cs₂CO₃ (12.5 mmol), dioxane (10 ml), reflux, 12 h

^bIsolated yield

We propose the following mechanism for the reaction. The first step is a copper-catalysed Hurltley-type arylation⁹ of the acetoacetic ester. The ketoester **5** can further react either *via* hydrolysis of the ester function followed by decarboxylation, yielding phenylacetone derivative **4**, or *via* a decarboxylation (retro-Claisen reaction) yielding ester **3**. In the presence of excess strong base the deacetylation process is preferred,¹⁰ especially in the presence of water (or ethanol)⁵ (see Figure 4). Nevertheless, in some cases ester hydrolysis may also occur as indicated by the lower yield of the respective ester product. However, the decarboxylated product **4** could not be isolated, or even identified by GC-MS or NMR analysis of the products.

Furthermore, the use of different bidentate *O,O*-, *O,N*- and *O,S*-ligands³ (e.g. benzoic acid derivatives) or amino acids² in the CuI catalysed arylation of CH-acids enhances the yield of arylacetic esters. In our case the products can act as such ligands and in the copper complexes formed the ester functions may be protected against hydrolysis. The complex forming ability of this catalyst has already been verified in the copper-catalysed transformation of aldoximes into nitriles¹¹ and nitriles into amides¹² where the complex formation of the catalyst with the aldoxime and acetonitrile, or with the nitrile and acetaldoxime, respectively, is the determining step of the reaction.

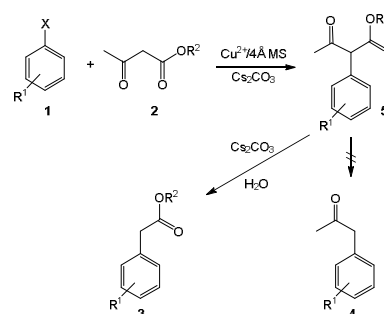


Figure 4

We also examined the reaction of iodobenzene with other CH-acids, however, acetylacetone, dimethyl malonate, and Meldrum's acid each proved to be unsuccessful. Comparing the pKa values¹³ of these CH-acids (Table 3) the lack of reactivity cannot be explained by the acidity of the substrate, since the pKa value of ethyl acetoacetate is between the values of dimethyl malonate and acetylacetone. In the case of dimethyl malonate and Meldrum's acid, the above mentioned hydrolysis of these esters might be too fast, while in case of acetylacetone the enolisation of the ketone might prevent reaction of the CH-acid function. Previously, a similar effect was observed in the reaction of acetylacetone with iodine in basic media.¹⁴

Table 3: CH-acids tested in the reaction^a

Entry	CH-acid	pKa ¹³	Conversion ^b (%)
1	ethyl acetoacetate	11	90
2	acetylacetone	9	0
3	dimethyl malonate	13	0
4	Meldrum's acid	5	0

^aAryl halide (5 mmol), ethyl acetoacetate (7.5 mmol), Cu²⁺/4Å MS (0.5 g, 0.1 mol% copper), Cs₂CO₃ 812.5 mmol, dioxane (10 ml), reflux, 12 h

^bBased on the GC-MS analysis of the product

GC-MS analysis of the reaction mixtures showed the presence of some characteristic and interesting by-products in small amounts. When iodobenzene was used, approximately 2-3% of diphenylether (**7**) was found. As the acid-base disproportionation of caesium bicarbonate produces water during the reaction, the formation of phenol and this by-product cannot be avoided (Figure 5). The formation of hydroxyester by-product (**9a**, <2%) can be explained by the aldol reaction between **4a** and ethyl acetoacetate, followed by a deacetylation (Figure 6).

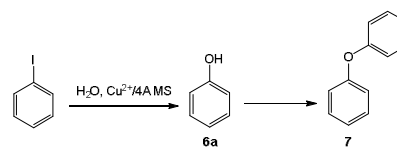


Figure 5

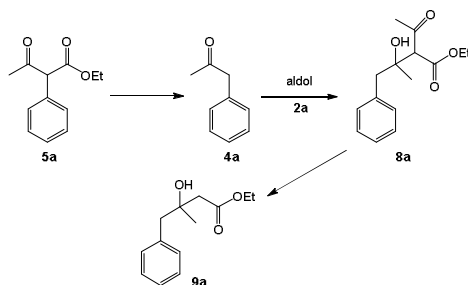


Figure 6

Interestingly, by-products **10a** and **10b** (Figure 7) were observed from the reactions of 3- and 4-iodotoluene, respectively, in very small amounts (approximately 1%). The proposed mechanism of their formation is shown using the example of 4-iodotoluene (Figure 8). In the presence of water, iodotoluene can form the appropriate phenol (**6b**) which then reacts with iodine (originating from oxidation of the formed CsI) yielding the intermediate benzyl iodide **11** which then alkylates the acetoacetate yielding **10b** (Figure 7).

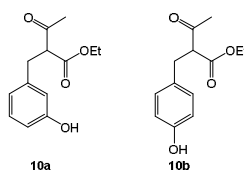


Figure 7

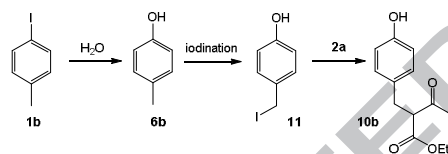


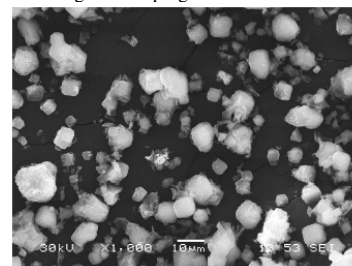
Figure 8

The reusability of the catalyst was also investigated. The solid filtered from the reaction mixture was washed with water then dichloromethane and heated at 150 °C for 2 h. Use of the recovered catalyst in the reaction of iodobenzene with ethyl acetoacetate yielded 60% of product. The large decrease in the yield could be explained by the precipitation of caesium iodide onto the surface of the catalyst. During the workup of the reaction this inorganic salt may not be removed completely from the surface, and thus it can cover and block the metal particles, decreasing the number of active sites.

Conclusion

In summary, a heterogeneous catalytic method has been developed for the selective preparation of arylacetic esters from ethyl acetoacetate and aryl iodides in the presence of copper(II) on 4Å molecular sieves. The catalyst can be easily removed from the reaction mixture, with no appreciable copper contamination of the product. The reaction time was considerably shorter than in the previously published homogeneous catalytic processes (12 h vs. 48 h).

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- GC-MS measurements were performed on an Agilent 6890 N-GC-5973 N-MSD chromatograph, using a 30 m × 0.25 mm Restek, Rtx-5SILMS column with a film layer of 0.25 μm. The initial temperature of column was 45 °C for 1 min, followed by programming at 10 °C/min up to 310 °C and a final period at 310 °C (isothermal) for 17 min. The temperature of the injector was 250 °C. The carrier gas was He and the operation mode was splitless. ¹H NMR spectra were made on BRUKER Avance-300 instrument using TMS as an internal standard in CDCl₃.
- Preparation and characterization of the catalyst: 4Å molecular sieves (2 g) and CuCl₂·2H₂O (0.34 g, 2 mmol) in deionized water (200 mL) were stirred at room temperature for 12 h. The light green solid was filtered, washed with deionized water (50 mL) and acetone (20 mL), then dried in an oven at 120 °C for 1 h. The copper content was experimentally determined as 5.8 wt% (by ICP-OES). 4ÅMS are a synthetic microporous sodium aluminosilicate (zeolite) having sodalite structure. During the impregnation copper ions can replace the sodium ions in the zeolite. Surface analysis by scanning electron microscope (SEM) showed cubic zeolite crystals (see picture below), most of the particles were in the 2.5–5 μm range. Energy-Dispersive X-ray Spectroscopy (EDS) showed that copper evenly covered the support's surface. Nitrogen adsorption measurements showed that the surface area of the original molecular sieves (810 m²/g) dropped to 360 m²/g after impregnation.



- General procedure: A mixture of aryl iodide (5 mmol), ethyl acetoacetate (7.5 mmol), Cu²⁺/4A (0.5 g, 0.1 mol% copper), and Cs₂CO₃ (12.5 mmol) in dioxane (10 ml) was stirred at 100 °C for 12 hours. The solid was filtered and the filtrate was evaporated in vacuo. The products were purified by column chromatography (silica gel, hexane:acetone 4:1 eluent). The products were characterized by ¹H-NMR and GC-MS.
- Selected analytical data: **Ethyl phenylacetate (3a)**: colourless liquid, ¹H NMR (300 MHz, CDCl₃) δ (ppm): 1.21 (t, 3H), 3.58 (s, 2H), 4.12 (q, 2H), 7.19-7.33 (m, 5ArH); MS: m/z: 164 (M⁺), 136, 119, 105, 91(100%), 77. **Diphenylether (7a)**: MS: m/z: 170(M⁺, 100%), 94, 77. **Ethyl 2-acetyl-3-hydroxy-3-methyl-4-phenylbutanoate (8a)**: MS: m/z: 248, 219, 203, 175(100%), 147, 131, 119, 102, 91, 77. **Ethyl 3-hydroxy-3-methyl-4-phenylbutanoate (9a)**: MS: m/z: 222(M⁺), 176, 149, 135, 107(100%), 91, 77. **Ethyl (4-hydroxybenzyl)acetoacetate (10b)**: MS: m/z:

236 (M^{*}), 207, 194, 190, 183, 177, 163, 155, 148, 138, 132,
121(100%), 115, 104, 91, 77.

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