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Chemoselective acylation of some oxidofunctionalised organolithium compounds

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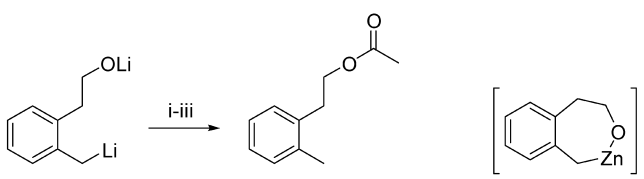
Abstract—Once oxidofunctionalised organolithium compounds **1** (easily prepared by reductive ring opening of isochroman and phthalan by DTBB-catalysed lithiation) were transmetallated with $ZnBr_2$/CuCN·2LiCl and reacted successively with a carboxylic acid anhydride and an acyl chloride in THF at 0°C, the corresponding differently acylated compounds **4** were obtained after hydrolysis with water. The anhydride performed the *O*-acylation exclusively and the acyl chloride carried out the *C*-acylation.

1. Introduction

The most important application of organometallic intermediates derived from main group metals in synthetic organic chemistry is focused on carbon–carbon bond forming reactions.[1] In addition, in many cases (i.e. the reaction of a Grignard reagent with a carbonyl compound) a new functionality is created at the same time. In this context, from a synthetic point of view, the use of functionalised organometallic compounds[2] plays a central role because the functionality present in the intermediate can be transferred to the electrophile, and in only a reaction step polyfunctionalised molecules can be prepared. Concerning the reactivity of these intermediates, the metal type results of great importance: for functionalised organolithium derivatives,[3] several problems appear derived from the compatibility between different functionalities and the carbon–lithium bond as well as from elimination processes, so they have to be prepared in many cases at very low temperatures. For less electropositive metals, such as functionalised organozinc compounds,[4] the functional compatibility is far higher but they are rather unreactive needing either very reactive electrophiles or the help of a transition metal as a catalyst. In the last decade we have been studying the preparation and synthetic applications of different functionalised organolithium compounds,[3] which are generated using an arene-catalysed lithiation at low temperature.[5] Following this strategy a number of saturated oxygen-, nitrogen- and sulfur-containing heterocycles of different size have been opened reductively giving the corresponding functionalised organolithium compounds.[3b] These intermediates react with electrophiles as expected, showing the typical behaviour for organolithium compounds.[6] For example, in the reaction with acylating reagents it is difficult to avoid overaddition to the corresponding ketone generated in situ, so usually the undesired tertiary alcohol is the main product, even working with a substoichiometric amount of the organolithium intermediate. For this reason, and in order to get the acylation, it would be of interest to exchange the lithium atom by other less reactive one, such as zinc.[7] In this paper we study the lithium–zinc transmetallation of some functionalised organolithium compounds and their reactivity towards acylating reagents.

2. Results and discussion

The reaction of the functionalised organolithium compound **1a** (easily prepared by reductive ring opening of commercially available isochroman with lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB))[8] with an equimolecular amount of zinc bromide in THF at 0°C followed by treatment with an excess of acetyl chloride (5 equiv.) at temperatures ranging between −78°C and room temperature led, after hydrolysis with water, to the corresponding *O*-acetylated product **2a** in almost quantitative yield (>90% by ^{1}H NMR) (Scheme 1). From



1a **2a** **I**

Scheme 1. *Reagents and conditions*: (i) $ZnBr_2$, THF, 0°C; (ii) MeCOCl (5 equiv.), −78°C to rt; (iii) H_2O.

Keywords: lithiation; lithium and compounds; zinc and compounds; acylation; catalysis.

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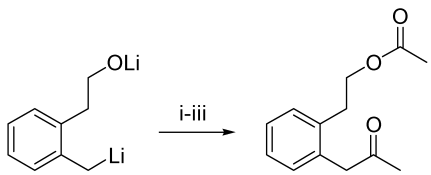


1a **3a**

Scheme 2. *Reagents and conditions*: (i) $ZnBr_2$, CuCN·2LiCl, THF, 0°C; (ii) MeCOCl (5 equiv.), −78°C to rt; (iii) H_2O.

Table 1. Reaction of intermediate **1a** with acylating agents

Entry	Acylating agent[a]	Reaction temperature (°C)[b]	Product[c]	
			No.	Yield (%)[d]
1	MeCOCl	−78 to rt	**3a**	50
2		−78	**3a**	32
3		0	**3a**	29
4		−78	**3a**	21[e]
5		−78	**2a**	90[f]
6	$(MeCO)_2O$	−78 to rt	**2a**	91
7			*d*-**2a**	90[g]

[a] Five equiv. were used unless otherwise stated.
[b] For the reaction step with the electrophile.
[c] Products **2a** and **3a** were ≥95% pure (300 MHz ^{1}H NMR and/or GLC).
[d] Isolated yields after column chromatography (silica gel, hexane/ethyl acetate) based on isochroman, the heterocyclic precursor of intermediate **1a**.
[e] Reaction performed with 2.5 equiv. of acetyl chloride.
[f] 10 mol% of CuCN·2LiCl was used.
[g] D_2O was used in the final quenching.

this result, it can be deduced that the organozinc intermediate of type **I** is not reactive enough to react at the carbanionic centre under the assayed reaction conditions.

We decided then to activate the organozinc intermediate by addition of a Cu(I) salt. Thus, using CuCN·2LiCl as the second metallic additive and under the same reaction conditions indicated in Scheme 1, the major product was the corresponding diacetylated one (**3a**),[9] being contaminated with variable amounts of the monoacetylated derivative **2a** (Scheme 2 and Table 1, entry 1). Other reaction conditions such as different temperatures or the use of a lesser amount (2.5 equiv.) of acetyl chloride gave lower yields (Table 1, entries 2–4). In addition, when a catalytic amount of the copper salt (10 mol%) was used, the only reaction product isolated was **2a** (Table 1, entry 5). Finally we tested acetic anhydride as the acylating reagent, finding that under the studied conditions compound **2a** was isolated in good yield (Table 1, entry 6). From the last result it seems that acetic anhydride is not reactive enough to produce the C-acylation. An additional reaction was performed using deuterium oxide as quenching agent, so we obtained the deuterated product *d*-**2a**, which is a proof that the corresponding organometallic intermediate was active before final quenching (Table 1, entry 7).

Once we knew the possibility of performing selectively the *O*- and *C*-acylation we studied the successive introduction of two different acyl groups in the intermediate **1a**. Thus, after transmetallation at 0°C as it was shown in Scheme 2, acetic anhydride (1.5 equiv.) was added at the same temperature for 15 min and the resulting mixture was then treated with an excess of propanoyl chloride at −78°C, compound **2a** being the only product isolated (89% yield). It was necessary to increase the temperature to 0°C in the reaction step with the second electrophile in order to get the expected compound **4a** (Table 2, entry 1 and Scheme 3). In the absence of the copper salt only compound **2a** was isolated in 90% yield. Finally, without $ZnBr_2$ only 28% of compound **4a** was obtained. With the aforementioned optimal conditions in hand, we studied the preparation of 'mixed' diacylated compounds **4** starting not only from compound **1a** but also from **1b** (easily obtained by ring opening of phthalan with the same methodology as for **1a**)[10] as it is shown in Scheme 3 and Table 2. In all cases the corresponding monoacylated 'reduced' products were obtained as by-products, resulting from both an *O*-acylation and a metal–hydrogen exchange.

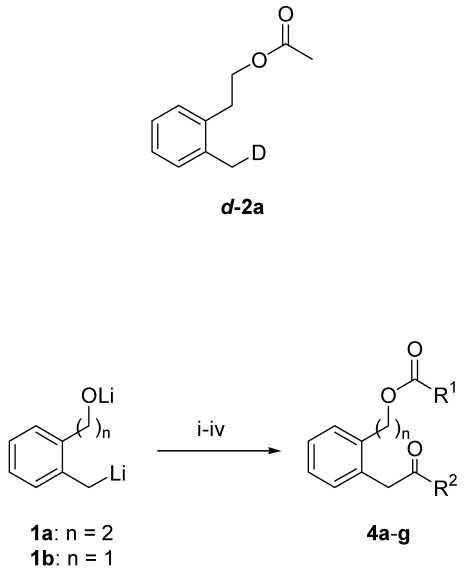
3. Conclusion

As a conclusion, we have reported here the chemoselective acylation of functionalised organolithium compounds of type **1**, through their corresponding zinc–copper intermediates. By using a carboxylic acid anhydride it is possible to perform exclusively the *O*-acylation, allowing these intermediates to carry out the corresponding *C*-acylation

Table 2. Preparation of compounds **4**

Entry	Starting Intermediate	Anhydride $(R^1CO)_2O$	Acyl halide R^2COCl	Product[a]			
				No.	R^1	R^2	Yield (%)[b]
1	**1a**	$(MeCO)_2O$	EtCOCl	**4a**	Me	Et	53
2	**1a**	$(EtCO)_2O$	PhCOCl	**4b**	Et	Ph	47
3	**1a**	$(Pr^nCO)_2O$	CyCOCl	**4c**	Pr^n	Cy[c]	45
4	**1a**	$(PhCO)_2O$	Bu^nCOCl	**4d**	Ph	Bu^n	39
5	**1b**	$(EtCO)_2O$	MeCOCl	**4e**	Et	Me	56
6	**1b**	$(Pr^nCO)_2O$	$4\text{-}ClC_6H_4COCl$	**4f**	Pr^n	$4\text{-}ClC_6H_4$	62
7	**1b**	$(PhCO)_2O$	$ClCH_2COCl$	**4g**	Ph	$ClCH_2$	41

[a] All products **4a–g** were >95% pure (GLC and/or 300 MHz ^{1}H NMR).
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the heterocycle, isochroman or phthalan, precursors of intermediates **1a** and **1b**, respectively.
[c] Cy=cyclohexyl.



Scheme 3. *Reagents and conditions*: (i) $ZnBr_2$, CuCN·2LiCl, THF, 0°C; (ii) $(R^1CO)_2O$ (1.5 equiv.), 0°C, 15 min; (iii) R^2COCl (5 equiv.), 0°C, 1 h; (iv) H_2O.

using an acyl chloride. Using this methodology two different acyl groups can be introduced chemoselectively in the molecule of the starting oxidofunctionalised organolithium compound.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere. FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker AC-300 with $CDCl_3$ as solvent and TMS as internal standard; chemical shifts (δ) are given in ppm and coupling constants (J) are given in Hz. Low resolution mass spectra (EI) were obtained at 70 eV on an Agilent 5973 Network spectrometer, fragment ions in m/z with relative intensities (%) in parentheses. High resolution mass spectra were obtained by the corresponding service at the University of Alicante using a Finnigan MAT 95 S apparatus. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett–Packard HP-4890 instrument equipped with a flame ionisation detector and a 30 m capillary column (0.25 mm diameter, 0.25 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{injector}$=275°C, T_{column}=80°C (3 min) and 80–270°C (15°C/min). Thin layer chromatography (TLC) was carried out on Merck plastic sheets coated with silica gel 60 F_{254}. Column chromatography was carried out using Merck 63–200 μm silica gel. All starting materials and solvents were commercially available (Acros, Aldrich, Fluka) of the best grade and were used without further purification. Lithium powder was prepared from commercially available lithium granules (99%, high sodium content, Aldrich) as it was already reported by us.[11] Zinc bromide was dried by heating at 130°C under reduced pressure (0.1 Torr) for 2 h before use.

4.2. DTBB-catalysed lithiation of isochroman and reaction of the corresponding organozinc derivative with acetyl chloride. Isolation of compound 2a

To a stirred green suspension of lithium powder (70 mg, 10 mmol) and DTBB (53 mg, 0.2 mmol) in THF (10 mL) was added dropwise isochroman (2 mmol) at room temperature, under an argon atmosphere. The colour disappeared after the addition, and after 30 min stirring the green colour appeared again. Then, the excess of lithium was filtered off under an inert atmosphere and the resulting solution was added to a solution of zinc bromide (450 mg, 2 mmol) in THF (5 mL). To the resulting mixture an excess of acetyl chloride (10 mmol) was added, either at −78°C or room temperature. After 1 h stirring, the reaction was hydrolysed with water (30 mL) at room temperature, acidified with 3 M HCl (6 mL) and extracted with ether (3×10 mL). The organic layer was washed with saturated NH_4Cl (2×10 mL), 4 M NaOH (2×10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated (15 Torr) to yield a residue, which was analysed by GLC and purified by column chromatography (silica gel, hexane/ethyl acetate) to give exclusively compound **2a**.

4.3. DTBB-catalysed lithiation of isochroman and reaction of the corresponding mixed zinc–copper derivative with acylating agents. Isolation of compounds 2a, 3a and *d*-2a

To a stirred green suspension of lithium powder (70 mg, 10 mmol) and DTBB (53 mg, 0.2 mmol) in THF (10 mL) was added dropwise isochroman (2 mmol) at room temperature, under an argon atmosphere. The colour disappeared after the addition, and after 30 min stirring the green colour appeared again. Then, the excess of lithium was filtered off under an inert atmosphere and the resulting solution was added to a solution of zinc bromide (450 mg, 2 mmol) in THF (5 mL). To the resulting mixture was added a solution of CuCN·2LiCl (prepared by dissolving copper (I) cyanide (180 mg, 2 mmol) and lithium chloride (85 mg, 4 mmol) in THF (10 mL)). The mixture was then cooled to the reaction temperature and after 10 min stirring the corresponding acylating agent (acetyl chloride or acetic anhydride, 10 mmol) was added. After 1 h stirring, the reaction was quenched with water (30 mL) or deuterium oxide (0.5 mL) at room temperature, acidified with 3 M HCl (6 mL) and extracted with ether (3×10 mL). The organic layer was washed with saturated NH_4Cl (2×10 mL), 4 M NaOH (2×10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated (15 Torr) to yield a residue, which was analysed by GLC and purified by column chromatography (silica gel, hexane/ethyl acetate) to give compounds **2a**, **3a** and *d*-**2a**.

4.4. DTBB-catalysed lithiation of isochroman and phthalan and successive reaction of the corresponding mixed zinc–copper derivatives with acid anhydrides and acyl chlorides. Isolation of compounds 4a–g

To a stirred green suspension of lithium powder (70 mg, 10 mmol) and DTBB (53 mg, 0.2 mmol) in THF (10 mL) was added dropwise phthalan or isochroman (2 mmol), at 0°C (for phthalan) or at room temperature (for isochroman),

under an argon atmosphere. The colour disappeared after the addition, and after 45 min stirring the green colour appeared again. Then, the excess of lithium was filtered off under an inert atmosphere and the resulting solution was added to a solution of zinc bromide (450 mg, 2 mmol) in THF (5 mL). To the resulting mixture was added a solution of CuCN·2LiCl (prepared by dissolving copper (I) cyanide (180 mg, 2 mmol) and lithium chloride (85 mg, 4 mmol) in THF (10 mL)). The mixture was then cooled with an ice bath and after 10 min stirring the corresponding acid anhydride (3 mmol) was added. After 15 min stirring, the corresponding acyl halide (10 mmol) was added and the mixture was stirred for 1 h at 0°C. The reaction was hydrolysed with water (30 mL), acidified with 3 M HCl (6 mL) and extracted with ether (3×10 mL). The organic layer was washed with saturated NH_4Cl (2×10 mL), 4 M NaOH (2×10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated (15 Torr) to yield a residue, which was analysed by GLC and purified by column chromatography (silica gel, hexane/ethyl acetate) to give compounds **4a**–**g**.

4.4.1. 2-(2-Methylphenyl)ethyl acetate (2a).[12] R_f 0.46 (hexane/ethyl acetate: 5:1); t_r 8.25 min; ν (film) 3064, 3019, 1494, 1461 (C=CH), 1740 (CO_2), 1239 cm^{-1} (C–O); δ_H 2.02 (s, 3H, CH_3CO_2), 2.33 (s, 3H, CH_3Ar), 2.93 (t, J=7.3 Hz, 2H, CH_2Ar), 4.24 (t, J=7.3 Hz, 2H, CH_2O), 7.13 (m, 4H, ArH); δ_C 19.2 (CH_3Ar), 20.9 (CH_3CO_2), 32.3 (CH_2Ar), 63.9 (CH_2O), 126.0, 126.6, 129.4, 130.2, 135.7, 136.3 (ArC), 170.9 (CO_2); m/z 119 (M^+-59, 12%), 118 (100), 117 (55), 105 (28). HRMS: M^+, found 178.1035; $C_{11}H_{14}O_2$ requires 178.0994.

4.4.2. 2-[2-(Deuteriomethyl)phenyl]ethyl acetate (*d*-2a). δ_C 18.9 (t, J_{CD}=19.2 Hz, 2H, CH_2D), 20.9 (CH_3CO_2), 31.3 (CH_2Ar), 64.0 (CH_2O), 126.0, 126.7, 129.4, 130.2, 135.7, 136.3 (ArC), 171.0 (CO_2); m/z 120 (M^+-59, 11%), 119 (100), 118 (84), 117 (25), 106 (28), 105 (13).

4.4.3. 2-[2-(2-Oxopropyl)phenyl]ethyl acetate (3a). R_f 0.25 (hexane/ethyl acetate: 5:1); t_r 11.19 min; ν (film) 3063, 3020, 1493, 1452 (C=CH), 1738 (CO_2), 1715 (CO), 1240 cm^{-1} (C–O); δ_H 2.03 (s, 3H, CH_3CO_2), 2.19 (s, 3H, CH_3CO), 2.88 (t, J=7.4 Hz, 2H, $ArCH_2CH_2$), 3.81 (s, 2H, $ArCH_2CO$), 4.20 (t, J=7.4 Hz, 2H, CH_2O), 7.12–7.15, 7.20–7.23 (2m, 1H and 3H, ArH); δ_C 20.8 (CH_3CO_2), 29.3 (CH_3CO), 31.9 ($ArCH_2CH_2$), 48.2 ($ArCH_2CO$), 64.2 (CH_2O), 127.0, 127.5, 129.9, 130.9, 133.1, 137.2 (ArC), 170.9 (CO_2), 206.2 (CO); m/z 160 (M^+-60, 43%), 145 (32), 135 (16), 118 (51), 117 (100), 115 (18), 105 (10), 91 (11). HRMS: M^+, found 220.1069; $C_{13}H_{16}O_3$ requires 220.1099.

4.4.4. 2-[2-(2-Oxobutyl)phenyl]ethyl acetate (4a). R_f 0.23 (hexane/ethyl acetate: 5:1); t_r 11.85 min; ν (film) 3063, 3021, 1492, 1453 (C=CH), 1739 (CO_2), 1716 (CO), 1240 cm^{-1} (C–O); δ_H 1.05 (t, J=7.3 Hz, 3H, CH_3CH_2), 2.03 (s, 3H, CH_3CO_2), 2.50 (q, J=7.3 Hz, 2H, CH_2CO), 2.89 (t, J=7.4 Hz, 2H, $ArCH_2CH_2$), 3.80 (s, 2H, $ArCH_2CO$), 4.20 (t, J=7.4 Hz, 2H, CH_2O), 7.12–7.26 (m, 4H, ArH); δ_C 7.7 (CH_3CH_2), 20.8 (CH_3CO_2), 31.9, 35.2 ($ArCH_2CH_2$ and CH_2CO), 47.0 ($ArCH_2CO$), 64.2 (CH_2O), 126.9, 127.3, 129.9, 130.8, 133.3, 136.1 (ArC), 170.9 (CO_2), 208.8 (CO); m/z 174 (M^+-60, 27%), 159 (14), 135 (11), 118 (27), 117 (37), 115 (11), 57 (100). HRMS: M^+, found 234.1313; $C_{14}H_{18}O_3$ requires 234.1256.

4.4.5. 2-[2-(2-Phenyl-2-oxoethyl)phenyl]ethyl propionate (4b). R_f 0.29 (hexane/ethyl acetate: 5:1); t_r 16.00 min; ν (film) 3062, 3023, 1493, 1449 (C=CH), 1736 (CO_2), 1689 (CO), 1184 cm^{-1} (C–O); δ_H 1.07 (t, J=7.5 Hz, 3H, CH_3), 2.26 (q, J=7.5 Hz, 2H, CH_2CO_2), 2.90 (t, J=7.3 Hz, 2H, $ArCH_2CH_2$), 4.25 (t, J=7.3 Hz, 2H, CH_2O), 4.39 (s, 2H, $ArCH_2CO$), 7.11–7.25, 7.42–7.57, 8.01–8.04 (3m, 4H, 3H and 2H, ArH); δ_C 8.8 (CH_3), 27.3, 32.1 ($ArCH_2CH_2$ and CH_2CO_2), 42.6 ($ArCH_2CO$), 64.0 (CH_2O), 126.7, 127.2, 128.1, 128.5, 129.7, 130.8, 133.0, 133.4, 136.3, 136.6 (12C, ArC), 174.1 (CO_2), 197.3 (CO); m/z 222 (M^+-74, 13%), 105 (100), 77 (21). HRMS: $M^+-[EtCO_2H]$, found 222.1048; $C_{16}H_{14}O$ requires 222.1045.

4.4.6. 2-[2-(2-Cyclohexyl-2-oxoethyl)phenyl]ethyl butyrate (4c). R_f 0.33 (hexane/ethyl acetate: 5:1); t_r 16.16 min; ν (film) 3063, 3021, 1492, 1451 (C=CH), 1732 (CO_2), 1713 (CO), 1175 cm^{-1} (C–O); δ_H 0.92 (t, J=7.4 Hz, 3H, CH_3), 1.22–1.45, 1.60–1.69, 1.78–1.89 (3m, 5H, 4H and 3H, $(CH_2)_5$ and CH_2CH_3), 2.27 (t, J=7.3 Hz, 2H, CH_2CO_2), 2.45–2.54 (m, 1H, CH), 2.85 (t, J=7.4 Hz, 2H, $ArCH_2CH_2$), 3.85 (s, 2H, $ArCH_2CO$), 4.21 (t, J=7.3 Hz, 2H, CH_2O), 7.08–7.10, 7.14–7.21 (2m, 1H and 3H, ArH); δ_C 13.6 (CH_3), 18.3, 25.5, 25.7, 28.6, 32.1, 36.1 (8C, $ArCH_2CH_2$, $CH_2CH_2CO_2$ and $(CH_2)_5$), 45.2 ($ArCH_2CO$), 50.2 (CH), 64.0 (CH_2O), 126.8, 127.2, 129.9, 130.8, 133.3, 136.3 (ArC), 173.5 (CO_2), 211.1 (CO); m/z 228 (M^+-88, 12%), 118 (10), 117 (15), 111 (38), 83 (100), 55 (24). HRMS: $M^+-[Pr^nCO_2H]$, found 228.1494; $C_{16}H_{20}O$ requires 228.1514.

4.4.7. 2-[2-(2-Oxohexyl)phenyl]ethyl benzoate (4d). R_f 0.31 (hexane/ethyl acetate: 5:1); t_r 17.27 min; ν (film) 3063, 3022, 1492, 1452 (C=CH), 1716 (CO_2 and CO), 1274 cm^{-1} (C–O); δ_H 0.87 (t, J=7.3 Hz, 3H, CH_3), 1.28 (sextet, J=7.4 Hz, CH_2CH_3), 1.56 (q, J=7.4 Hz, 2H, CH_2CH_2CO), 2.49 (t, J=7.4 Hz, 2H, CH_2CO), 3.03 (t, J=7.4 Hz, 2H, $ArCH_2CH_2$), 3.84 (s, 2H, $ArCH_2CO$), 4.46 (t, J=7.4 Hz, 2H, CH_2O), 7.13–7.31, 7.34–7.58, 8.00–8.03 (3m, 4H, 3H and 2H, ArH); δ_C 13.7 (CH_3), 22.2, 25.8, 32.1, 41.8 ($CH_2CH_2CH_2$ and $ArCH_2CH_2$), 47.4 ($ArCH_2CO$), 64.7 (CH_2O), 127.0, 127.4, 128.2, 128.3, 129.4, 130.0, 130.8, 132.9, 133.2, 136.2 (12C, ArC), 166.4 (CO_2), 208.5 (CO); m/z 202 (M^+-122, 38%), 118 (49), 117 (28), 115 (11), 105 (72), 85 (100), 77 (38), 57 (66). HRMS: $M^+-[PhCO_2H]$, found 202.1366; $C_{14}H_{18}O$ requires 202.1357.

4.4.8. 2-(2-Oxopropyl)phenylmethyl propionate (4e). R_f 0.21 (hexane/ethyl acetate: 5:1); t_r 11.12 min; ν (film) 3061, 3025, 1495, 1456 (C=CH), 1738 (CO_2), 1716 (CO), 1175 cm^{-1} (C–O); δ_H 1.12 (t, J=7.5 Hz, 3H, CH_2CH_3), 2.17 (s, 3H, CH_3CO), 2.32 (q, J=7.5 Hz, 2H, CH_2CH_3), 3.81 (s, 2H, $ArCH_2CO$), 5.07 (s, 2H, CH_2O), 7.17–7.40 (m, 4H, ArH); δ_C 8.9 (CH_2CH_3), 27.3 (CH_2CH_3), 29.4 (CH_3CO), 47.9 ($ArCH_2CO$), 64.2 (CH_2O), 127.4, 128.8, 130.2, 130.9, 133.6, 134.5 (ArC), 173.9 (CO_2), 205.7 (CO); m/z 146 (M^+-74, 12%), 105 (10), 104 (100), 57 (16). HRMS: $M^+-[EtCO]$, found 163.0791; $C_{10}H_{11}O_2$ requires 163.0759.

4.4.9. 2-[2-(4-Chlorophenyl)-2-oxoethyl]phenylmethyl butyrate (4f). R_f 0.35 (hexane/ethyl acetate: 5:1); t_r 17.02 min; ν (film) 3067, 3027, 1488, 1456 (C=CH), 1736 (CO_2), 1692 (CO), 1171 cm^{-1} (C–O); δ_H 0.86 (t, J=7.4 Hz, 3H, CH_3), 1.56 (m, 2H, CH_2CH_3), 2.18 (t, J=7.4 Hz, 2H, CH_2CO_2), 4.38 (s, 2H, $ArCH_2CO$), 5.09 (s, 2H, CH_2O), 7.15–7.46, 7.95–7.98 (2m, 6H and 2H, ArH); δ_C 13.6 (CH_3), 18.2, 35.9 ($CH_2CH_2CO_2$), 42.5 ($ArCH_2CO$), 64.2 (CH_2O), 127.5, 128.7, 128.9, 129.7, 130.1, 130.9, 133.5, 134.6, 134.8, 139.7 (12C, ArC), 173.1 (CO_2), 195.8 (CO); m/z 242 (M^+-88, 11%), 141 (29), 139 (90), 111 (27), 105 (12), 104 (100). HRMS: $M^+-[Pr^nCO]$, found 243.0546; $C_{15}H_{12}ClO$ requires 243.0577.

4.4.10. 2-(3-Chloro-2-oxopropyl)phenylmethyl benzoate (4g). R_f 0.22 (hexane/ethyl acetate: 5:1); t_r 16.17 min; ν (film) 3065, 3031, 1494, 1452 (C=CH), 1716 (CO_2 and CO), 1271 cm^{-1} (C–O); δ_H 4.07, 4.10 (2s, 2H and 2H, CH_2COCH_2), 5.32 (s, 2H, CH_2O), 7.20–7.54 (m, 7H, ArH), 7.99 (d, J=8.0 Hz, 2H, ArH); δ_C 43.9, 47.9 (CH_2COCH_2), 64.8 (CH_2O), 127.9, 128.4, 129.1, 129.5, 129.6, 130.6, 131.0, 132.4, 133.1, 134.5 (12C, ArC), 166.2 (CO_2), 199.6 (CO); m/z 145 (M^+-157, 10%), 120 (16), 117 (10), 105 (100), 104 (22), 103 (12), 77 (31). HRMS: $M^+-[PhCO]$, found 197.0358; $C_{10}H_{10}ClO_2$ requires 197.0369.

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References

1. See, for instance: In *Organometallics in Synthesis. A Manual*; 2nd ed. Schlosser, M., Ed.; Wiley: Chichester, 2002.
2. For a review, see: Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 4414–4435.
3. For reviews, see: (a) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155–181. (b) Nájera, C.; Yus, M. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 67–96. (c) Yus, M.; Foubelo, F. *Rev. Heteroatom Chem.* **1997**, *17*, 73–107. (d) Nájera, C., Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867–926.
4. For reviews, see: (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188. (b) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC: Boca Raton, 1996. (c) In *Organozinc Reagents: A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford University: New York, 1999. (d) Knochel, P.; Millot, N.; Rodríguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417–731. For a recent paper, see: (e) Huo, S. *Org. Lett.* **2003**, *5*, 423–425.
5. For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155–161. (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–237. (c) Yus, M. *Synlett* **2001**, 1197–1205. (d) Yus, M.; Ramón, D. J. *Lat. J. Chem.* **2002**, 79–92. (e) Ramón, D. J.; Yus, M. *Rev. Cubana Quím.* **2002**, *14*, 75–115. (f) Yus, M. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2003.
6. See, for instance: (a) Wakefield, B. J. *Organolithium Methods*; Academic: London, 1988. (b) In *Lithium Chemistry. A Theoretical and Experimental Overview*; Sapse, A.-M., von Ragué Schleyer, P., Eds.; Wiley: Chichester, 1995. (c) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002.
7. For former studies on similar processes from our laboratory, see: (a) Yus, M.; Pastor, I. M.; Gomis, J. *Tetrahedron* **2001**, *57*, 5799–5805. (b) Yus, M.; Gomis, J. *Tetrahedron Lett.* **2001**, *42*, 5721–5724. (c) Yus, M.; Gomis, J. *Eur. J. Org. Chem.* **2002**, 1989–1995. (d) Yus, M., Gomis, J. *Eur. J. Org. Chem.*, **2003**, 2043–2048.
8. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3365–3374.
9. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3351–3364.
10. A similar result was obtained in our laboratory using a lithium–copper transmetallation, being in this case necessary to use HMPA as cosolvent: Pastor, I. M.; Yus, M. *Tetrahedron* **2001**, *57*, 2371–2378.
11. Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* **2001**, *57*, 10119–10124.
12. Chuchani, G.; Rotinov, A.; Caraballo, D. F.; Medina, J. D. *React. Kinet. Catal. Lett.* **1980**, *13*, 173–177.