SHORT PAPER

J. Chem. Research (S),
2003, 374–376

Microwave-promoted synthesis of β-hydroxyesters by the Reformatsky reaction in the absence of solvent[†]

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A microwave-promoted Reformatsky reaction of aldehydes and ketones with ethyl bromoacetate, in the absence of solvent, using activated zinc metal and solid NH_4Cl afforded the corresponding β-hydroxyesters in good to excellent yields.

Keywords: β-hydroxyester, Reformatsky reaction

The Reformatsky reaction, in which a carbonyl compound is reacted with an α-haloester in the presence of zinc metal to furnish the corresponding β-hydroxyester, is regarded as one of the most fundamental reactions for carbon–carbon bond formation. β-Hydroxyesters[1] are widely utilised as one of the most important intermediates in organic synthesis.[2]

In modern synthetic organic chemistry, efforts are directed towards fast, safe, inexpensive and environmentally friendly developments. In this regard a reaction in a wet solvent, an aqueous medium or an ionic liquid, which has practical viability is useful. One of the major current challenges before chemists is to develop synthetic methodologies where optimal value of resources is achieved and consumption of energy is minimised. To achieve these goals the use of microwave energy has been found to be useful. Rapid, ecofriendly chemical transformations[3] with excellent yields have resulted and there have been many reports[4] of remarkable decreases in reaction time for the reactions carried out under microwave irradiation using domestic microwave ovens.

Recently, several modified Reformatsky reactions using other reagents such as silicon, tin, indium, zinc-copper couple, potassium graphite, *etc.* have been described.[5] Moreover, the application of sonochemistry as one of the techniques for synthesising β-hydroxyesters, via the Reformatsky reaction, using trimethylborate or activated zinc metal, along with promoters such as iodine and potassium iodide, as a co-solvent has also been studied.[6] There is also a recent report on the indium-mediated[5s] Reformatsky reaction under ultrasonic irradiation as a beneficial method for the synthesis of β–hydroxyesters. Application of the Reformatsky reaction, under ultrasound, to Schiffs bases and nitriles leads to the formation of β-lactams[7] and keto-γ-butyrolactones[8] respectively, in fair yields. However, this modification is seldom of general applicability. Microwave-induced organic reactions are usually carried out in a solvent medium such as DMF, halogenated aromatic compounds, alcohols, glycol ethers, *etc.* or on a solid support such as M^{n+}-montomorillonite (phyllosilicate), silica and alumina, in which no solvent is used.

Results and discussion

We now describe the synthesis of β-hydroxyesters by a microwave-assisted (MW) Reformatsky reaction of aldehydes and ketones with ethyl bromoacetate, in the absence of solvent, using activated zinc metal and solid NH_4Cl.

To find the optimal conditions for a microwave-assisted Reformatsky reaction, these reactions were carried out in a domestic Kenstar Microwave Oven OM-9918C (450W). Microwave-assisted reaction conditions were superior because in the absence of microwaves, the Reformatsky reaction of benzaldehyde, in refluxing dry benzene, occurred more slowly (2 hours) and yield of the corresponding β-hydroxyester was just 65%.

Table 1 summarises the experimental results and illustrates the efficiency and scope of the present method. For the aromatic aldehydes, the presence of various substituents (Table 1, entries 2, 3 and 4) on the aromatic ring showed little effect on the efficiency of the reactions. The protocol developed here was also applied to reaction with ketones.

Experimental

Caution: Although we did not experience any kind of problem, it is normally recommended that the use of metals in a microwave oven be avoided. The use of metals is potentially very dangerous since metals heat up to spectacular temperatures and sharp fragments can cause arcing thereby damaging the oven and creating a fire or burn hazard.

All experiments were carried out in a domestic Kenstar Microwave Oven OM-9918C (450W), without subjecting the oven to any modifications. IR spectra were recorded on a Perkin Elmer 1310 instrument while ^1H NMR spectra were recorded on a Brucker AC 300F NMR spectrometer (300MHz) with TMS as an internal standard. Silica gel (60–120 mesh) was used for chromatographic separation and silica gel-G was used for TLC.

Representative procedure: A mixture of carbonyl compound (1mmol), ethyl bromoacetate (3mmols), Zn dust (0.5g) and NH_4Cl (1.0g) was thoroughly ground in a mortar, transferred to a 25ml conical flask and placed in a microwave oven (Kenstar OM-9918C, 450W) for the specified time **(**Table 1**)**. The reaction mixture was then treated with saturated aq. NH_4Cl solution (25ml) and finally extracted with diethyl ether (2 × 25ml). The combined organic extracts were washed with water (2 × 10ml), brine (2 × 10ml) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure followed by purification using silica gel chromatography (hexane: ethyl acetate = 5:1) afforded the desired β-hydroxyesters in good to excellent yields.

Ethyl 3-hydroxy-3-phenylpropanoate (**1**): Oil (lit.[9] b.p. 128 °C/4 torr); ^1H NMR ($CDCl_3$) δ: 7.05–7.22, m, 5H; 4.96, t (*J*=6Hz), 1H; 3.98, q (*J*=7Hz), 2H; 3.46, br s, 1H; 2.48, d (*J*=6Hz), 2H; 1.12, t (*J*=7Hz), 3H. IR (film) ν_{max}: 3500, 2955, 1710, 1605, 1460, 1350, 1280, 1235 cm^{-1}.

Ethyl 3-hydroxy-3-(4-methylphenyl)propanoate (**2**): Oil (lit.[9] b.p. 142 °C/8 torr); ^1H NMR ($CDCl_3$) δ: 7.05, d (*J*=8Hz), 2H; 6.96, d (*J*=8Hz), 2H; 4.95, t (*J*=6Hz), 1H; 4.07, q (*J*=6.5Hz), 2H; 3.30, br s, 1H; 2.55, d (*J*=6Hz), 2H; 2.35, s, 3H; 1.22, t (*J*=6.5Hz), 3H. IR (film) ν_{max}: 3500, 2960, 1725, 1605, 1460, 1345, 1290, 1225 cm^{-1}.

Ethyl 3-hydroxy-3-(4-methoxyphenyl)propanoate (**3**): Oil (lit.[9] b.p. 163 °C/7.5 torr); ^1H NMR ($CDCl_3$) δ: 7.30, d (*J*=8Hz), 2H; 6.85, d (*J*=8Hz), 2H; 5.04, t (*J*=6.5Hz), 1H; 4.10, q (*J*=7Hz), 2H; 3.80, s, 3H; 3.24, br s, 1H; 2.64, d (*J*=6.5Hz), 2H; 1.25, t (*J*=7Hz), 3H. IR (film) ν_{max}: 3450, 2970, 1715, 1600, 1460, 1365, 1295, 1240 cm^{-1}.

Ethyl 3-hydroxy-3-(4-chlorophenyl)propanoate (**4**): Oil (lit.[9] Oil); ^1H NMR ($CDCl_3$) δ: 7.31, br s, 4H; 5.10, t (*J*=5.5Hz), 1H; 4.17, q (*J*=7Hz), 2H; 3.65, br s, 1H; 2.58, d (*J*=5.5Hz), 2H; 1.26, t (*J*=7Hz), 3H. IR (film) ν_{max}: 3400, 2930, 1695, 1470, 1375, 1280, 1260 cm^{-1}.

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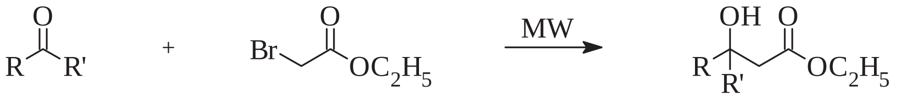
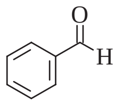
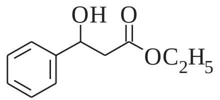
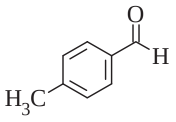
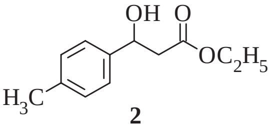
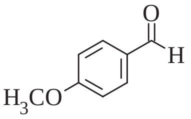
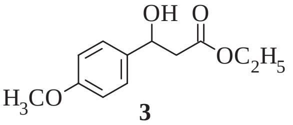
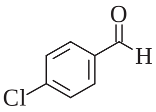
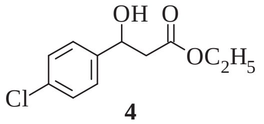
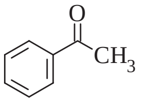
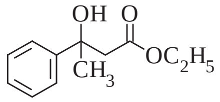
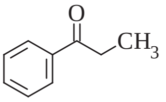
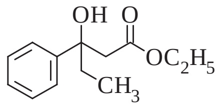
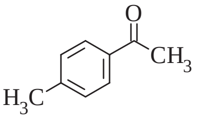
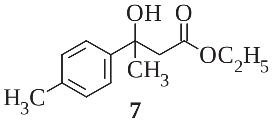
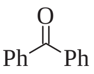
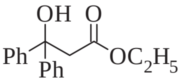
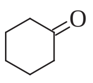
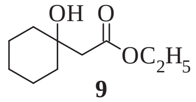
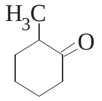
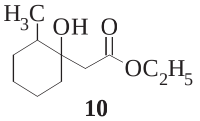
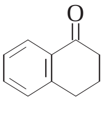
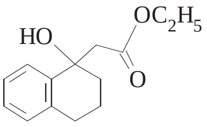
[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Preparation of β-hydroxyesters of carbonyl compounds by using activated Zn dust, ethyl bromoacetate and NH_4Cl



R = -Alk, -Ar
R' = -Alk, -Ar, -H

Entry	Compound	Time/s	Product[a]	Yield/%
1		50	 **1**	92
2		50	 **2**	90
3		55	 **3**	95
4		50	 **4**	92
5		55	 **5**	92
6		60	 **6**	90
7		60	 **7**	92
8		50	 **8**	95
9		60	 **9**	92
10		60	 **10**	92
11		50	 **11**	90

[a] All products were characterised by IR, ^1H NMR and compared with authentic samples.

Ethyl 3-hydroxy-3-phenylbutanoate (**5**): Oil (lit.[10] b.p. 50–60 °C/3 torr); ^{1}H NMR ($CDCl_3$) δ: 7.24–7.82, m, 5H; 4.35, br s, 1H; 4.02, q (*J*=6Hz), 2H; 3.10, d (*J*=16.5Hz), 1H; 2.88, d (*J*=16.5Hz), 1H; 1.50, s, 3H; 1.22, t (*J*=6Hz), 3H. IR (film) ν_{max}: 3500, 2940, 1725, 1460, 1365, 1290, 1265 cm^{-1}.

Ethyl 3-hydroxy-3-phenylpentanoate (**6**): Oil (lit.[11] Oil); ^{1}H NMR ($CDCl_3$) δ: 7.10–7.38, m, 5H; 4.22, br s, 1H; 3.98, q (*J*=6.5Hz), 2H; 2.96, d (*J*=16Hz), 1H; 2.78, d (*J*=16Hz), 1H; 1.76–1.84, m, 2H; 1.08, q (*J*=6.5Hz), 3H; 0.82, t (*J*=7Hz), 3H. IR (film) ν_{max}: 3510, 2955, 1720, 1460, 1355, 1270, 1250 cm^{-1}.

Ethyl 3-hydroxy-3-(4-methylphenyl)butanoate (**7**): Oil (lit.[12] Oil); ^{1}H NMR ($CDCl_3$) δ: 7.20, d (*J*=8Hz), 2H; 6.99, d (*J*=8Hz), 2H; 4.15, q (*J*=6.5Hz), 2H; 3.39, br s, 1H; 2.69–2.64, m, 2H; 2.35, s, 3H; 1.60, s, 3H; 1.30, t (*J*=6.5Hz), 3H. IR (film) ν_{max}: 3410, 2960, 1715, 1510, 1440, 1390, 1295, 1240 cm^{-1}.

Ethyl 3,3-diphenyl-3-hydroxypropanoate (**8**): Oil (lit.[10] b.p. 70–75 °C/1 torr); ^{1}H NMR ($CDCl_3$) δ: 7.20–7.12, brs, 10H; 4.12, q (*J*=7Hz), 2H; 3.10, br s, 1H; 2.85–2.80, m, 2H; 1.30, t (*J*=7Hz), 3H. IR (film) ν_{max}: 3410, 2960, 1715, 1510, 1440, 1390, 1290, 1245 cm^{-1}.

Ethyl 1-hydroxycyclohexylacetate (**9**): Oil (lit.[12] Oil) ^{1}H NMR ($CDCl_3$) δ: 4.18, q (*J*=6Hz), 2H; 3.05, brs, 1H; 2.40–2.34, m, 2H; 1.55–1.50, m, 4H; 1.46–1.38, m, 6H; 1.28, t (*J*=6Hz), 3H. IR (film) ν_{max}: 3420, 2955, 1705, 1460, 1295, 1235 cm^{-1}.

Ethyl 2-methyl-1-hydroxycyclohexylacetate (**10**): Oil (lit.[13] b.p. 75–82 °C/0.5 torr); ^{1}H NMR ($CDCl_3$) δ: 4.22, q (*J*=6.5Hz), 2H; 3.10, brs, 1H; 2.36–2.30, m, 2H; 1.68–1.64, m, 1H; 1.55–1.50,m, 2H; 1.46–1.38, m, 6H; 1.30, t (*J*=6.5Hz), 3H; 1.06, d (*J*=7.6Hz), 3H. IR (film) ν_{max}: 3440, 2950, 1718, 1490, 1385, 1280, 1235 cm^{-1}.

Ethyl 1-hydroxy-1,2,3,4-tetrahydro-napthalen-1-ylacetate (**11**): Oil (lit.[14] b.p. 130 °C/0.6 torr); ^{1}H NMR ($CDCl_3$) δ: 7.03–6.90, m, 4H; 4.15, q (*J*=7.5Hz), 2H; 3.18, brs, 1H; 2.92–2.88, m, 2H; 2.74–2.69, m, 2H; 1.72–1.64, m, 4H; 1.26, t (*J*=7.5Hz), 3H. IR (film) ν_{max}: 3460, 2955, 1725, 1510, 1445, 1380, 1288, 1230 cm^{-1}.

The authors are grateful to the Principal and the Head of the Department of Chemistry, Ismail Yusuf College, Mumbai for their support and constant encouragement and Dr A.R Joseph for helpful suggestions.

Received 1 December 2002; accepted 12 March 2003
Paper 02/1713

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