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Magnesium Monoperphthalate (MMPP): a Convenient Oxidant for the Direct Rubottom Oxidation of Malonates, β-Keto Esters, and Amides

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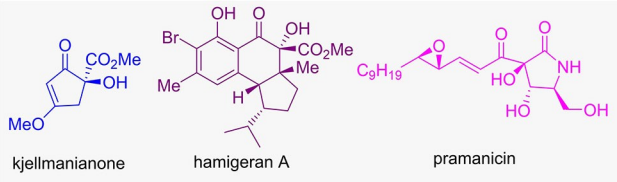
Dedicated to Professor Franco Cozzi on the occasion of his 70th birthday.

A mild and convenient protocol for the α-hydroxylation of α-substituted malonates, β-ketoesters, and β-ketoamides is disclosed. Cheap and stable magnesium monoperphthalate (MMPP) was effective for a first direct α-hydroxylation protocol of the Rubottom oxidation, providing tartronic esters, cyclic α-hydroxy β-ketoesters and amides in good to high yields, when working at room temperature and in ethanol as the solvent. The protocol has been successfully scaled up to gram quantity.



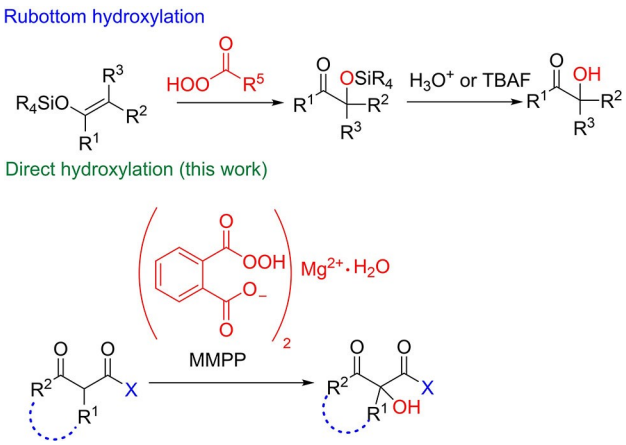
Scheme 1. Examples of biologically active α-hydroxy-β-ketoesters and amides.

The α-hydroxy carbonyl unit is a recurrent motif, found in several bioactive compounds, pharmaceuticals and synthetically useful intermediates, exemplified by antibiotics kjellmanianone,[1] hamigeran A[2] and antimicrobial agent pramanicin (Scheme 1).[3]

Moreover, α-hydroxy malonates, known as tartronic esters, demonstrated to be useful building blocks for the synthesis of drugs,[4] or bioderived intermediates for surfactant preparation.[5] Unsurprisingly, direct α-hydroxylation of the corresponding 1,3-dicarbonyl compounds was intensively investigated as the most straightforward process to prepare these compounds.[6] Hence, numerous methodologies have been developed over the last decades, mostly based on enolate oxidation with different systems, including MoOPH,[7] Fe/H_2O_2,[8] Ni/dimethyl dioxirane (DMDO),[9] MCPBA,[10] ROOH,[11] Oxone,[12] Ce/O_2,[13] IBX,[14] oxazirines.[15] The search for simple and inexpensive methodologies, proceeding under convenient conditions, using green solvents at room temperature and readily available oxidants, has become an imperative to follow in modern oxidation chemistry.[16]

The direct α-hydroxylation of α-substituted β-dicarbonyl compounds, such as β-ketoesters/amides and malonates, has been accomplished by a variety of oxidative systems, except the most common laboratory oxidant such as MCPBA.[10] Indeed, competitive oxidations can occur, affecting the selectivity and applicability, thus the use of their silyl enol ethers as alternative starting reagents is required (Scheme 2).[10b]

This transformation, well-known as the Rubottom reaction,[17] although being a widespread and useful α-hydroxylation reaction in organic synthesis,[18] requires prederivatization of carbonyl compounds to silyl enol ethers and occasionally TBAF deprotection of the firstly formed silyl ether, which represent drawbacks from the step-economic point of view. In this context, magnesium monoperphthalate (MMPP),[19] although being cheaper, stable and practical peroxy acid than popular MCPBA, was only briefly studied by Gannon and House



Scheme 2. Routes for peroxy acid mediated α-hydroxylation of carbonyl compounds.

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in the direct oxidation of two α-substituted β-diketones.[20] The oxidation proved to be unselective, observing the formation of α-hydroxy-β-diketones, together with the carboxylic acids and α-hydroxy ketones. Although these results were not encouraging, as part of our interest in the α-hydroxylation of β-dicarbonyl compounds[21] and considering the practical features of MMPP as an oxidant, we undertook an investigation focused on the hydroxylation of α-substituted malonates, β-ketoesters and amides. We herein report the preliminary results, showing the suitability of MMPP to serve as a useful and practical oxidant in the direct hydroxylation reaction, working under green conditions.

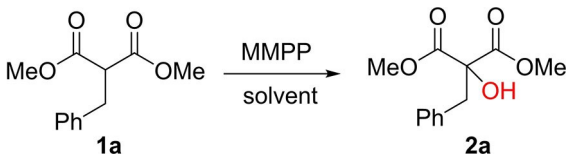
First, the optimization of model 2-benzyl malonate methyl ester **1a** was studied (Table 1). The reaction was carried out with 2 equivalents of the oxidant at 70 °C in MeOH, being MMPP more soluble in polar media (entry 1). Pleasingly, after a short time, α-hydroxylated product **2a** was isolated in 64% yield. Reducing the amount of MMPP (1.2 equiv) drastically retarded the conversion to the product to only 10% (entry 1 in parenthesis). Hence, the reactions were successively performed with 2 equivalents of MMPP. The oxidation could be carried out at room temperature to give **2a** in 58% yield after 16 hours (entry 2). Under more concentrated conditions, the conversion to **2a** was significantly accelerated (entry 3), although further concentration of the reaction mixture, was not useful (entry 4). At this point, green polar solvents were checked in the oxidation performed at C = 0.5 M of reagent **1a** (entries 5–7). Unfortunately, the hydroxylation did not proceed in dimethyl carbonate (DMC), ethyl acetate and in water using tetrabutyl ammonium chloride $(n\text{Bu})_4\text{NCl}$ as phase transfer catalyst.

Interestingly, when using 96% ethanol (entry 8) or anhydrous ethanol (entry 9) after a short reaction time, product **2a** was isolated in 88% and 87% yield, respectively. Pleasingly, in both cases, only a small amount (≈10%) of the transesterification α-hydroxylated product, was observed. These results are noteworthy, since they indicate that transesterification of different malonate esters would not occur when using EtOH as the solvent. In order to reduce the amount of MMPP to 1 equivalent, inorganic bases (1 equiv) were added, with the aim to help enolization, working in anhydrous ethanol. Pleasingly, good conversions were observed, after reasonable reaction times, when using Na_2CO_3 and NaOH (entries 10 and 11). The use of 96% ethanol with NaOH provided lower conversion to product **2a** (entry 12). Pleasingly, when using $NaHCO_3$ in anhydrous ethanol, compound **2a** was recovered in 84% yield (entry 13). Given the presence of two peroxyacid molecules in the MMPP salt, 0.5 equivalent of MMPP was used in the oxidation (entry 14). After a comparable reaction time, the product was isolated in 66% yield, suggesting that 1 equivalent of MMPP is required to achieve higher conversion to the product. Finally, MCPBA was checked in the hydroxylation of **1a** either in the presence or absence of $NaHCO_3$ (entries 15 and 16). The results confirmed MCPBA to be an unsuitable oxidant, given the presence of unreacted **1a** in the reaction mixture.

With the optimized conditions in hands, a variety of α-substituted malonates was investigated under the conditions reported in entry 13 of Table 1 (Table 2).

Different α-alkyl substituted tartronic esters **2a–d** were isolated in good yields.[22] α-Functionalized malonates were also converted into the α-hydroxyl derivatives **2e–h** in fairly good yields. The α-allyl substituted diethyl malonate **1i** was then subjected to oxidation to check the chemoselectivity of MMPP. The α-hydroxylated product **2i** was recovered as prevalent compound in 52% yield, whereas product of further oxidation,

Table 1. Optimization of the α-hydroxylation of malonate ester **1a**.

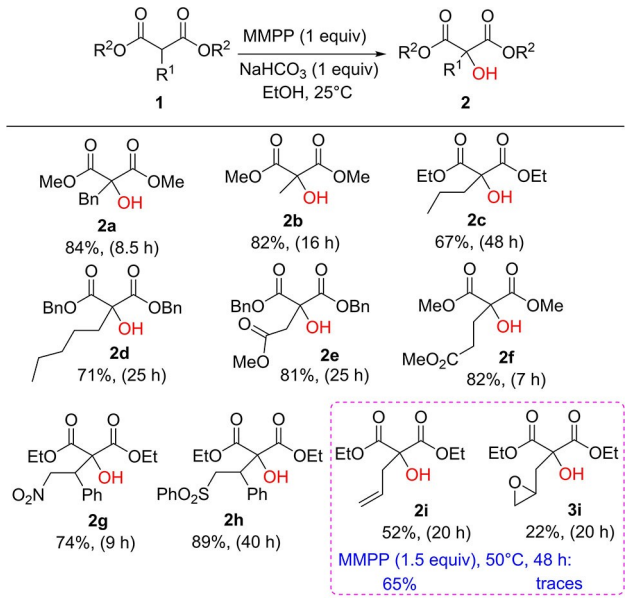


1a **2a**

Entry[a]	Solvent	Additive	Conditions	**2a** [%][b]
1	MeOH	–	70 °C/3 h(5 h)[c]	64(10)[c]
2	MeOH	–	25 °C/16 h	58
3[d]	MeOH	–	25 °C/5.5 h	68
4[e]	MeOH	–	25 °C/4 h	59
5[d]	DMC	–	25 °C/24 h	nd
6[d]	AcOEt	–	25 °C/24 h	–
7[d]	H_2O	TBAC 20 mol%	25 °C/7 h	–
8[d]	EtOH 96%	–	25 °C/4 h	88
9[d]	EtOH	–	25 °C/4 h	87
10[d,f]	EtOH	Na_2CO_3 (1 equiv)	25 °C/7 h	73
11[d,f]	EtOH	NaOH (1 equiv)	25 °C/3.5 h	69
12[d,f]	EtOH 96%	NaOH (1 equiv)	25 °C/4 h	60
13[d,f]	EtOH	$NaHCO_3$ (1 equiv)	25 °C/8.5 h	84
14[d,g]	EtOH	$NaHCO_3$ (1 equiv)	25 °C/8.5 h	66
15[h]	EtOH	$NaHCO_3$ (1 equiv)	25 °C/6 h	–
16[h]	EtOH	–	20 °C/16 h	–

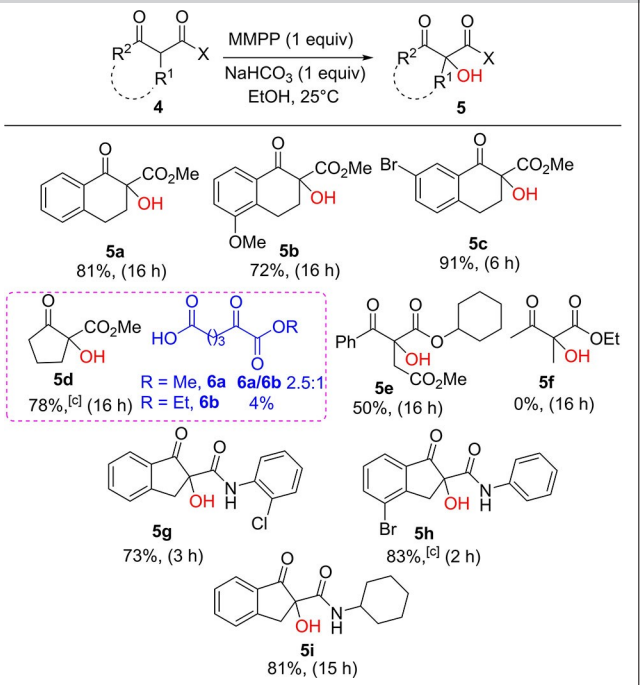
[a] Reaction conditions: **1a** (89 mg, 0.4 mmol), MMPP (technical ≈80%, 495 mg, 2 equiv) in 4 mL of solvent (at C = 0.1 M [**1a**]). [b] Isolated yield after chromatography. [c] MMPP (1.2 equiv) was used. [d] Reaction performed at C = 0.5 M [**1a**]. [e] Reaction performed at C = 1 M [**1a**]. [f] MMPP (1.0 equiv) was used. [g] MMPP (0.5 equiv) was used. [h] MCPBA (1.0 equiv) was used.

Table 2. Scope of the α-hydroxylation of malonate esters **1** to tartronic esters **2**.[a,b]



[a] Reaction conditions: **1** (0.4 mmol), MMPP (technical ≈80%, 247 mg, 1 equiv), $NaHCO_3$ (34 mg, 1 equiv) in anhydrous EtOH (0.8 mL) at C = 0.5 M [**1**]. [b] Isolated yield after chromatography.

Table 3. Scope of the α-hydroxylation of β-keto esters and amides **4**.[a,b]



[a] Reaction conditions: **4** (0.4 mmol), MMPP (technical ≈80%, 247 mg, 1 equiv), $NaHCO_3$ (34 mg, 1 equiv) in anhydrous EtOH (0.8 mL) at C = 0.5 M [**4**]. [b] Isolated yield after chromatography. [c] MMPP (0.5 equiv) was used.

the epoxy alcohol **3i**, was isolated in 22% yield. Notably, the oxidation proved to be chemoselective when carried out using 1.5 equivalents of MMPP at 50 °C. Indeed, compound **2i** was isolated in 65% yield[22] and traces of epoxy alcohol **3i** were detected. This result might be ascribed to increased enolization of the reagent and then faster epoxidation of more nucleophilic enol moiety (see Scheme 4). Interestingly, MMPP displayed reversed chemoselectivity in the oxidation of compound **1i** with respect to DMDO.[23,9b] Indeed, DMDO did not provide compound **2i**, but the oxidation of terminal carbon-carbon double bond occurred selectively to give the epoxide. Then, further oxidation of epoxide with DMDO yielded product **3i**. Notably, MMPP appears to be the sole oxidant useful to obtain the tartronic ester **2i** in chemoselective manner.[24]

The study was then extended to α-substituted β-ketoesters and amides. Under the optimized conditions, some cyclic β-keto esters underwent α-hydroxylation to give the products **5a–c** in good to high yields (Table 3). In the case of sensitive cyclopentanone based β-keto ester **4d**, the reaction was carried out using 0.5 equivalent of MMPP. The expected product **5d** was isolated in 78%, observing only traces of further oxidative cleavage side-products **6a/6b**.[25]

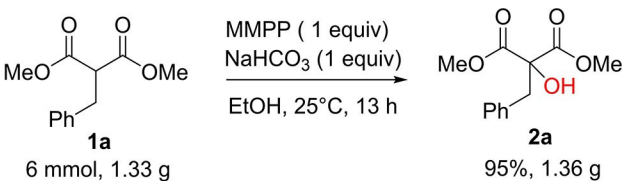
Acyclic α-substituted cyclohexyl 3-oxo-3-phenylpropanoate underwent the oxidation to compound **5e** in 50% yield.

Unfortunately, α-methyl ethyl acetoacetate **4f** did not provide the expected compound, but further oxidation to low molecular side-products was observed. Secondary aryl and alkyl substituted β-ketoamides were converted into the hydroxylated products **5g–i** in fairly good yields.

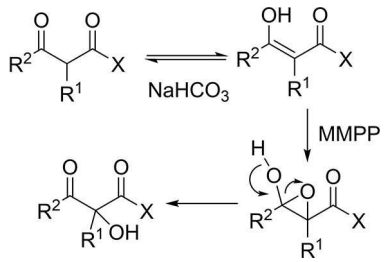
Finally, to study the applicability of this oxidative system, model reaction on compound **1a** was scaled up to 6 mmol (Scheme 3). Pleasingly, after slightly prolonged reaction time, compound **2a** was isolated in excellent yield, demonstrating the efficiency of MMPP mediated hydroxylation on a larger scale. The result is of interest, considering that in contrast to MCPBA, MMPP is a non-shock-sensitive and non-deflagrating peroxy acid, with improved water solubility, making easier the work-up procedure.

Ester analogues of compound **2a**, obtained by α-hydroxylation reaction of the corresponding malonates, have been used by a Merck group as key-intermediates for the synthesis of nonsteroidal mineralocorticoid receptor antagonists.[26]

The oxidation is thought to proceed via the generally accepted one-pot Rubottom type-oxidation (Scheme 4).[6a,10b] Enol tautomer of the starting 1,3-dicarbonyl compound, whose presence is fostered by the basic additive, is epoxidized by MMPP. The hydroxyl epoxide intermediate then rearranges to the final α-hydroxy derivative.



Scheme 3. Scale-up of the model reaction on compound **1a**.



Scheme 4. Mechanism of hydroxylation mediated by MMPP.

In conclusion, we disclosed a simple and useful methodology for the direct α-hydroxylation of malonates, β-ketoesters and amides by MMPP, which proceeds at room temperature in EtOH as green solvent. To the best of our knowledge this is a first example of Rubottom hydroxylation, which do not require prederivatization of the β-dicarbonyl compounds to silyl enol ethers. Commercially available oxidant MMPP furnished the products in good to high yields, achieving comparable results also at gram-scale. This work adds to the list of oxidative reactions enabled by using MMPP[19b,27] as a practical and mild peroxy acid with a distinctive and advantageous behavior with respect to MCPBA.[28] Further investigations on the reactivity of MMPP, in direct hydroxylation reactions, are underway in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Green solvents · Hydroxylation · β-Ketoesters · MMPP · Tartronic esters

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