



α -Hydroxylation of malonates under mild reaction conditions

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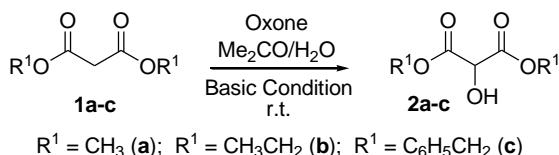
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INTRODUCTION

Peroxyulfuric acid and its potassium salt have been known as oxidizing agents for some time. The potassium peroxymonosulfate salt, sold under the commercial name Oxone® ($2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$), is a very stable substance and can be easily handled. Oxone has been used in the oxidation of alcohols and C-H bonds, and also in the epoxidation of olefins.¹ In this work, we present a simple method to prepare α -hydroxy malonates of synthetic interest.

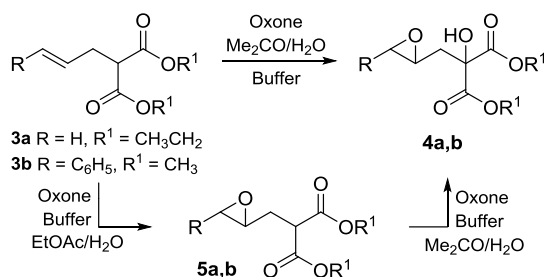
RESULTS AND DISCUSSION

For unsubstituted malonates **1a-c** (Scheme 1), the hydroxylation of the α -carbon was achieved in a short period (15 to 60 minutes) using the mild conditions² presented in Table (entries 1-3). The ¹H NMR data show good conversion to the products **2a-c**, although the recovery of **1a** and **1b** was difficult due to their solubility in water.



Scheme 1. Hydroxylation of unsubstituted malonates **1**.

Malonates containing double bonds tethered to the α -carbon, such as allyl (**3a**) and cinnamyl (**3b**), underwent epoxidation and hydroxylation in a single step (Scheme 2 and Table, entries 4 and 5).

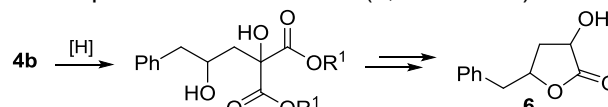


Scheme 2. Hydroxylation and epoxidation of allyl- (**3a**) and cinnamyl-substituted malonates (**3b**).

The hydroxylation of the allyl-substituted malonate **3a** was not complete within 48 hours, giving a 1:1 mixture of epoxide **5a** and hydroxylated epoxide **4a**. With cinnamyl-substituted malonate **3b**, the epoxidation with α -hydroxylation occurred faster (4

hours) and with better conversion than with **3a**. Epoxides **5a** and **5b** were also suitable starting materials for the synthesis of α -hydroxylated epoxides **4a,b** under basic condition (for example, entry 6). The utilization of phosphate buffer is due to its ideal pH for the reaction with oxone (pH ~ 8.0)¹ and the maintenance of the pH even when 2.5 equiv. Oxone was employed.

The hydroxylated epoxide **4b** is of synthetic interest as the building block for the short synthesis of the natural product harzialactone³ (**6**, Scheme 3).



Scheme 3. Synthesis of harzialactone (**6**) from **4b**.

Table. Hydroxylation of malonates **1**, **3** and **5**

#	Malonate	Oxone (Equiv.)	Basic Cond.	Prod.	Conv. (%) ^a
1	1a	1.3	NaHCO_3^b	2a	100
2	1b	1.3	NaHCO_3^b	2b	100
3	1c	1.3	NaHCO_3^b	2c	100
4	3a	2.5	Buffer ^c	4a	50 ^d
5	3b	2.5	Buffer ^c	4b	100
6	5a	1.3	Buffer ^c	4a	100

^a Conversion was determined by ¹H NMR integration (200 MHz).

^b 4.7 equiv. of base was employed.

^c Buffer = 1 mol L⁻¹ $\text{K}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$, pH 8.

^d Formation of the hydroxylated epoxide **4b**.

CONCLUSION

The hydroxylation of malonates **1** and **3** at the α -carbon was achieved under mild conditions. The substituted malonates required buffer basic condition due to its better pH maintenance, giving hydroxylated epoxides **4**. The optimization of the reaction conditions and the extension of this method to other substrates are under investigation.

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