

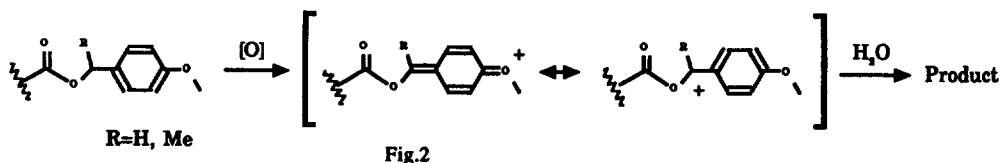
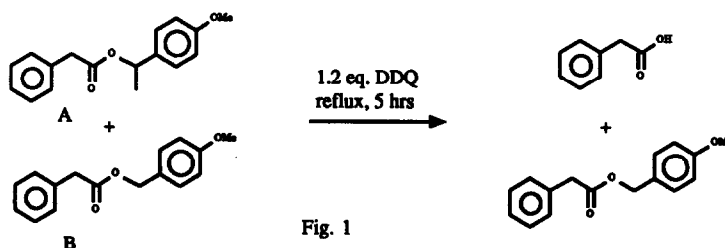
## OXIDATIVE DEBENZYLATION OF 4-METHOXY- $\alpha$ -METHYLBENZYL ESTERS

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**Summary:** 4-Methoxy- $\alpha$ -methylbenzyl alcohol was introduced as a new protecting group for carboxylic acids. 4-Methoxy- $\alpha$ -methyl benzyl esters obtained from the coupling of 4-methoxy- $\alpha$ -methylbenzyl alcohol and corresponding acids, were hydrolyzed in good yield by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). This process is compatible with several functional groups which are vulnerable to the reductive debenzylation reaction.

Needs for an efficient protection and deprotection scheme for highly functionalized carboxylic acid derivatives are still in demand.<sup>1</sup> A number of protecting groups have been introduced with some degree of limitations because of their intrinsic problems.<sup>2</sup> For example, a benzyl ester is one of the most widely used protected forms for carboxylic acids because of its stability to acids and bases and to a number of common organic reagents and yet it can be easily removable under the neutral condition such as a catalytic hydrogenation. However, this process is not compatible with various reducible functional groups such as nitros and olefins. Kim and Misco<sup>3</sup> have reported an oxidative cleavage reaction of 2,6-dimethoxybenzyl esters by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)<sup>4</sup> based on the well established benzylic oxidation by DDQ.<sup>5</sup> However we found that 4-methoxy- $\alpha$ -methylbenzyl esters were more readily cleavable by DDQ and had some additional advantages over the simple benzyl esters. Herein we would like to report our results on 4-methoxy- $\alpha$ -methylbenzyl esters as the better protecting group for carboxylic acids.

4-Methoxy- $\alpha$ -methylbenzyl esters examined in this study were obtained from the coupling of 4-methoxy- $\alpha$ -methylbenzyl alcohol and corresponding acids with dicyclohexylcarbodiimide (DCC).



Introduction of one methyl group on the benzylic position provided several distinct advantages over the simple benzyl group. First of all, the reactivity toward the oxidative cleavage reaction increases quite substantially from the fact that under the deprotection condition only the compound A was converted to the corresponding carboxylic acid (Fig.1). This is most likely due to the stabilizing effect of the methyl group on the cationic intermediate (Fig.2).

After testing various ring substituents and their position on the phenyl ring, we found that  $\alpha$ -methylbenzyl alcohol with one methoxy group on either ortho or para position of the phenyl ring is satisfactory (Fig.3). Therefore we selected 4-methoxy- $\alpha$ -methylbenzyl alcohol and examined the oxidative deprotection reaction and the result is summarized in Table 1.

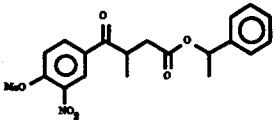
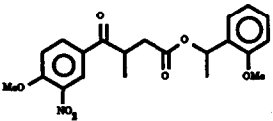
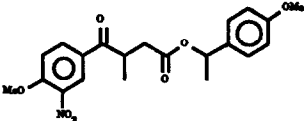
Substrate	Condition (1.2 eq. DDQ)	Yield
	reflux, 10 hrs	no reaction
	reflux, 7 hrs	85 %
	room temp., 8 hrs	88 %

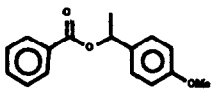
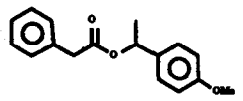
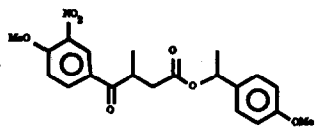
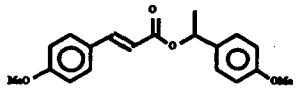
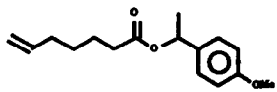
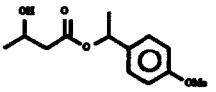
Fig.3

Simple aromatic and aliphatic esters hydrolyzed quite nicely to give the corresponding acids in good yield (entry 1 & 2). A functional group compatibility of this process has been examined with the compounds containing reduction sensitive functional groups, such as a nitro group (entry 3), a conjugated olefin (entry 4) and an isolated olefin (entry 5), and these groups were found to be inert under this condition. Even acid/base sensitive  $\beta$ -hydroxy ester could be cleaved nicely to give the corresponding  $\beta$ -hydroxy acid (entry 6).

We also found that the deprotection condition is mild enough to preserve the chirality of a rather sensitive compound and that was demonstrated by using optically active compound C. The compound C was coupled with a racemic 4-methoxy- $\alpha$ -methylbenzyl alcohol as usual and subjected the resulting ester to the oxidative deprotection condition and found the compound C with a full optical activity (Fig.4). This finding would provide a possibility that optically active 4-methoxy- $\alpha$ -methylbenzyl alcohol<sup>7</sup> could be utilized for the resolution of racemic carboxylic acids by separating the diastereoisomers of the resulting ester.

In conclusion we are introducing 4-methoxy- $\alpha$ -methylbenzyl alcohol as a new protecting group for carboxylic acids. The oxidative deprotection condition is mild, neutral and the work-up procedure is quite simple. Carboxylic acids with sensitive functional groups and epimerizable centers can be protected with this reagent.

Table 1

Entry	Substrate	Condition	Yield
(1)		reflux, 8 hrs	90 %
(2)		reflux, 5 hrs	86 %
(3)		rt, 8 hrs	88 %
(4)		reflux, 15 hrs	92 %
(5)		reflux, 15 hrs	82 %
(6)		reflux, 9 hrs	47 %

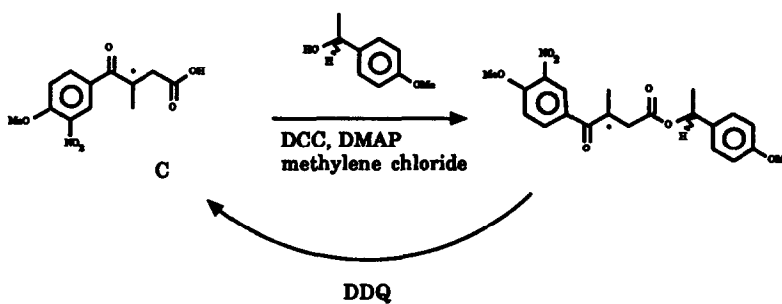


Fig. 4

A typical deprotection procedure is as follow;

To a solution of the ester (4.01g) (entry 3) in methylene chloride (50ml) and H<sub>2</sub>O (3ml) was added DDQ (2.95g, 1.2 eq.) portionwise over 5 min. at room temperature. The resulting mixture was stirred at room temperature for 8 hours. The reaction mixture was dried with anhydrous sodium sulfate and filtered. After the concentration of the filtrate under reduced pressure, the residue was purified by column chromatography (hexane: ethyl acetate=1:1, then 5% MeOH in dichloromethane, 70-230 mesh silica gel) to afford the corresponding acid (2.35g,88% yield).

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### References and Notes

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- The reaction proceeded cleanly. The low yield is due to the solubility of the product in water during the work-up.
- Optically active 4-methoxy- $\alpha$ -methylbenzyl alcohol was prepared as follow;

