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# A Convenient Preparation of p-Methoxybenzyl Esters

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# A CONVENIENT PREPARATION OF *p*-METHOXYBENZYL ESTERS

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**Abstract:** Carboxylic acids are conveniently and efficiently protected as their *p*-methoxybenzyl esters under very mild conditions using the pre-formed reagent *N,N'*-diisopropyl-*O*-(4-methoxybenzyl)isourea, and this method allows selective protection of carboxylic acids in the presence of other functionalities such as enolisable ketones and alcohol groups.

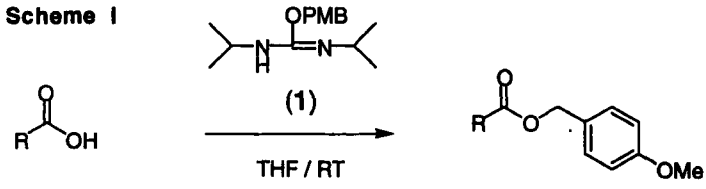
## Introduction

The *p*-methoxybenzyl (PMB) group has found wide application as an ether protecting group,[1,2] and allows a choice of selective deprotection strategies, for example by using dichlorodicyanoquinone (DDQ)[3] or ceric ammonium nitrate (CAN)[4] oxidation. The use of PMB as a carboxylic acid protecting group has not been so well developed, due mainly to problems in formation of the PMB esters. Literature methods need either prior activation of the carboxylic acids,[5] or have the problem of generating by-products which are difficult to separate.[6,7]

## Results and Discussion

Here we report the application of the new reagent *N*,*N*'-diisopropyl-*O*-(4-methoxybenzyl)isourea **1** (PMB isourea) as a very mild and efficient reagent for protection of the carboxylic acid functionality. The PMB isourea **1** was prepared by adapting the literature method used to prepare the benzyl alcohol analogue[8], by reacting *p*-methoxybenzyl alcohol with *N*,*N*'-diisopropylcarbodiimide in the presence of a catalytic amount of copper (I) chloride. The identity of the resultant PMB isourea **1** was confirmed by its characteristic IR absorption band at 1660 $cm^{-1}$, and the reagent was used directly without further purification.

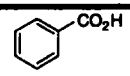
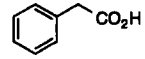
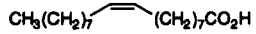
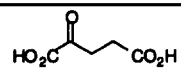
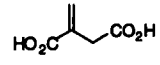
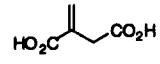
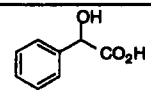
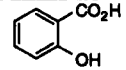
**Scheme 1**




Reaction of a range of carboxylic acids with **1** (requiring from 1.1 to 1.5 eq) at ambient temperature in THF afforded the corresponding esters in high yield (Scheme 1). Other commonly used solvents such as acetone and acetonitrile can also be used for this reaction where solubility of the acid in THF is a problem. When the reaction was attempted using methanol as the solvent some of the corresponding *p*-methoxybenzyl methyl ether was also formed as a by-product, although the reaction is generally tolerant of hydroxy groups in the substrate.

Ester derivatisation of a variety of carboxylic acids using the PMB isourea **1** under these very mild conditions was examined and the results shown in Table1. This demonstrates the utility of the method for various types of carboxylic acid such as aliphatic acids (entry 2-5), acrylic acids (entry 7-8) and aromatic acids (entry 1,10). As expected the mild reaction conditions leave an olefinic linkage undisturbed (entry 4,5), and an enolisable carbonyl group is also unaffected

**Table 1** Preparation of PMB esters using the PMB isourea reagent

| Entry | Acid | Formula | Isourea (eq) | % Yield Ester |
|---|---|---|---|---|
| 1 | Benzoic |  | 1.3 | 100 |
| 2 | Phenylacetic |  | 1.3 | 97 |
| 3 | Palmitic | $CH_3(CH_2)_{14}CO_2H$ | 1.3 | 99 |
| 4 | Elaidic |  | 1.3 | 99 |
| 5 | Oleic |  | 1.3 | 92 |
| 6 | 2-Ketoglutaric |  | 2.6 | 62 (diester) |
| 7 | Itaconic |  | 3.0 | 78 (diester) |
| 8 | Itaconic |  | 1.1 | 61 (monoester)[a] |
| 9 | Mandelic |  | 1.3 | 82 |
| 10 | Salicylic |  | 1.5 | 85 |

[a]Monoester obtained as a 1:1 mixture of regioisomers

(entry 6). Importantly, under these mild conditions a hydroxy group (entry 9,10) is tolerated whether aliphatic or phenolic, and in the case of mandelic acid or salicylic acid no ether by-products were detected. The formation of the *p*-methoxybenzyl methyl ether from methanol was presumably due to its large excess concentration when it was used as solvent. Dicarboxylic acids can either be diprotected (6,7), or monoprotected (entry 8) by varying the amount of PMB isourea used. Under mono protection conditions dicarboxylic acids such as 2-ketoglutaric acid or itaconic acid gave a mixture of both regioisomeric monoesters with no regioselectivity observed.

In conclusion we have found that the PMB isourea **1** reacts under mild conditions with a wide variety of carboxylic acids to produce the corresponding PMB esters in high yields. The PMB protecting group is easily removed using either DDQ[3] or CAN[4] oxidation in high yields (>80%), which gives the PMB ester group advantages over other protecting groups for mild and selective protection and deprotection strategies.



## Experimental

*Preparation of N,N'-diisopropyl-O-(4-methoxybenzyl) isourea* **1**.

*p*-Methoxybenzyl alcohol (22.1g, 0.16 mol) was added slowly to an ice-cooled mixture of copper (I) chloride (60 mg) in *N,N'*-diisopropylcarbodiimide (20.4 g, 0.16 mol). The resulting slightly green suspension was stirred for an additional 1 h at 0 °C then left overnight at RT. The mixture was diluted with petroleum ether (bp 40-60, 100 ml), then filtered through a pad of alumina. Evaporation of the solvent gave the desired compound **1** as a colourless liquid (33.6 g, 80%): IR $\nu_{max}$ $cm^{-1}$ (film) 3443 (Ar-H, and N-H), and 1660 (O-C=NH); $\delta_H$ (360 MHz; $CDCl_3$) 0.9 (6 H, d, *J* 7.7 Hz, $C\underline{H}_3CH$), 1.0 (6 H, d, *J* 7.7 Hz, $C\underline{H}_3CH$), 3.2 (1 H, m, $CH_3C\underline{H}$), 3.45 (1 H, bs, NH), 3.78 (1 H, m, $CH_3C\underline{H}$), 3.80 (3 H, s, $OCH_3$), 5.02 (2 H, s, $ArCH_2$), 6.87 (2 H, d, *J* 8.6 Hz, ArH), and 7.32 (2 H, d, *J* 8.6 Hz, ArH); $\delta_C$

(90 MHz, $CDCl_3$) 23.96, 24.28, 43.36, 46.21, 55.17, 66.41, 71.40, 113.55, 129.34, 151.53, and 158.95; m/e (FAB) 265 ($MH^+$), 121 ($M^+$-143, 100%), and 58 ($M^+$-206).

*General p-methoxybenzyl ester preparation procedure.*

To a solution of the carboxylic acid (1 eq) in THF (or acetone, $CH_3CN$) was added the PMB isourea **1** (1.3 eq) and the reaction mixture stirred at RT overnight. The white solid that formed (the isopropyl urea by-product) was removed by filtration, and the filtrate concentrated *in vacuo*. Chromatographic purification on silica gel afforded the desired PMB ester.

The following p-methoxybenzyl esters (shown in Table 1) were prepared using this general procedure:

***p*-Methoxybenzyl benzoate** $^1H$ NMR ($CDCl_3$) δ 3.8 (3 H, s, $OCH_3$), 5.3 (2 H, s, $ArCH_2$), 6.8-8.5 (9 H, m, Ar-H); $^{13}C$ NMR ($CDCl_3$) δ 55.35, 66.61, 114.04, 128.23, 128.41, 129.74, 130.14, 130.33, 133.01, 159.73, 166.57; MS (EI) m/z 242 ($M^+$), 121 ($M^+$-121, 100%); HRMS Found $M^+$ 242.0899; $C_{15}H_{14}O_3$ requires $M^+$ 242.0939.

***p*-Methoxybenzyl phenylacetate** $^1H$ NMR ($CDCl_3$) δ 3.6 (2 H, s, $CH_2$), 3.8 (3 H, s, $CH_3$), 5.1 (2 H, s, $CH_2O$), 6.8-7.2 (9 H, m, Ar-H); MS (EI) m/z 256 ($M^+$), 121 ($M^+$-135, 100%); HRMS Found $M^+$ 256.1123; $C_{16}H_{16}O_3$ requires $M^+$ 256.1099.

***p*-Methoxybenzyl palmitate** m.p. 46-46.5 $^0C$; UV $\lambda_{max}$ (Hexane) 227 nm (log ε 4.2), 274 nm (log ε 3.4), 280 nm (log ε 3.4); $^1H$ NMR ($CDCl_3$) δ 0.8 (3 H, t, *J* 6.5 Hz, $CH_3$), 1.2 (24 H, bs, 12 x $CH_2$), 1.6 (2 H, m, $C\underline{H}_2CH_2CO$), 2.3 (2 H, t, *J* 7.5 Hz, $CH_2CO$), 3.8 (3 H, s, $OCH_3$), 5.0 (2 H, s, $CH_2$), 6.8 (2 H, d, *J* 8.7 Hz, Ar-H), 7.2 (2 H, d, *J* 8.7 Hz, Ar-H); MS (EI) m/z 376 ($M^+$), 121 ($M^+$-255, 100%);

HRMS Found $M^+$ 376.2973; $C_{24}H_{40}O_3$ requires $M^+$ 376.2977. Anal Calc for $C_{24}H_{40}O_3$ requires C, 76.5; H, 10.7; Found: C, 76.8; H, 10.7.

***p*-Methoxybenzyl elaidate** m.p. 28.5-29 $^0$C; UV $\lambda_{max}$ (Hexane) 226 nm (log ε 4.1), 274 nm (log ε 3.2), 280 nm (log ε 3.2); $^1$H NMR ($CDCl_3$) δ 0.8 (3 H, t, *J* 6.4 Hz, $CH_3$), 1.2 (22 H, bs, 11 x $CH_2$), 1.7 (2 H, m, $C\underline{H}_2CH_2CO$), 1.9 (4 H, m, $C\underline{H}_2CH{=}CHC\underline{H}_2$), 2.2 (2 H, t, *J* 7.5 Hz, $CH_2CO$), 1.7 (2 H, m, $C\underline{H}_2CH_2CO$), 1.9 (2H, m, CH=CH), 6.8 (2 H, d, *J* 8.7 Hz, Ar-H), 7.2 (2 H, d, *J* 8.7 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$) δ 14.18, 22.75, 24.99, 29.00, 29.15, 29.37, 29.56, 29.70, 31.97, 32.61, 32.67, 34.42, 55.31, 65.93, 113.97, 128.34, 130.07, 130.26, 130.51, 159.62, 170.69; MS (EI) m/z 402 ($M^+$), 121 ($M^+$-281, 100%); HRMS Found $M^+$ 402.3154; $C_{26}H_{42}O_3$ requires $M^+$ 402.3134.

***p*-Methoxybenzyl oleate** $^1$H NMR ($CDCl_3$) δ 0.8 (3 H, t, *J* 6.5 Hz, $CH_3$), 1.2 (22 H, bs, 11 x $CH_2$), 1.6 (2 H, m, $C\underline{H}_2CH_2CO$), 2.0 (4 H, m, $C\underline{H}_2CH{=}CHC\underline{H}_2$), 2.2 (2 H, t, *J* 7.5 Hz, $CH_2O$), 3.8 (3 H, s, $OCH_3$), 5.0 (2 H, s, $CH_2O$), 5.3 (2 H, m, CH=CH), 6.8 (2 H, d, *J* 8.7 Hz, Ar-H), 7.2 (2 H, d, *J* 8.7 Hz, Ar-H); MS (EI) m/z 402 ($M^+$), 121 ($M^+$-381, 100%); HRMS Found $M^+$ 402.3179; $C_{26}H_{42}O_3$ requires $M^+$ 402.3134.

**1,5-Di(4-methoxybenzyl) 2-ketoglutarate** $^1$H NMR ($CDCl_3$) δ 2.7 (2 H, t, *J* 6.5 Hz, $CH_2$), 3.2 (2 H, t, *J* 6.5 Hz, $CH_2$), 3.8 (6 H, s, $OCH_3$), 5.1 (2 H, s, $OCH_2$), 5.2 (2 H, s, $OCH_2$), 6.8-7.4 (8 H, m, Ar-H); MS (EI) m/z 386 ($M^+$), 121 ($M^+$-265, 100%); HRMS Found $M^+$ 386.1363; $C_{21}H_{22}O_7$ requires $M^+$ 386.1366.

**1,4-Di(4-methoxybenzyl) itaconate** $^1$H NMR ($CDCl_3$) δ 3.5 (2 H, s, $CH_2$), 3.7 (6 H, s, 2 x $OCH_3$), 5.0 (2 H, s, $OCH_2$), 5.1 (2 H, s, $OCH_2$), 5.7 (H, s, =C$\underline{H}$), 6.4 (H, s, =C$\underline{H}$), 6.8 (4 H, d, *J* 9.9 Hz, Ar-H), 7.3 (4 H, d, *J* 9.8 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$) δ 37.86, 55.27, 66.53, 66.63, 113.96, 128.26, 128.79, 130.11, 133.90,

158.43, 166.05, 170.66; FAB-MS m/z 370 ($M^+$), 121 ($M^+$-249, 100%); HRMS Found $M^+$ 370.1409; $C_{21}H_{22}O_6$ requires $M^+$ 370.1416.

***p*-Methoxybenzyl itaconate monoester** $^1$H NMR ($CDCl_3$) δ 3.2 (2 H, s, $CH_2$), 3.7 (3 H, s, $OCH_3$), 5.1 (2 H, s, $OCH_2$), 5.6 (H, s, =C<u>H</u>), 6.2 (H, s, =C<u>H</u>), 6.8 (4 H, d, *J* 9.9 Hz, Ar-H), 7.2 (4 H, d, *J* 9.8 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$) δ 37.60, 55.24, 66.45, 113.89, 127.99, 128.38, 129.87, 134.22, 159.53, 166.17, 170.76; FAB-MS m/z 370 ($M^+$), 121 ($M^+$-249, 100%); HRMS Found $M^+$ 250.2469; $C_{13}H_{14}O_5$ requires $M^+$ 250.2473.

***p*-Methoxybenzyl mandelate** $^1$H NMR ($CDCl_3$) δ 3.7 (3 H, s, $CH_3$), 4.8 (2 H, s, $OCH_2$), 5.1 (1 H, s, CH), 6.9 (2 H, d, *J* 8.7 Hz, Ar-H), 7.1 (2 H, d, *J* 8.7 Hz, Ar-H), 7.2-7.4 (5 H, m, Ar-H); $^{13}$C NMR ($CDCl_3$) δ 54.80, 65.21, 72.50, 113.22, 126.50, 127.38, 127.98, 128.53, 133.00, 140.02, 159.91, 174.21; FAB-MS m/z 272 ($M^+$), 121 ($M^+$-151, 100%); HRMS Found $M^+$ 272.1056; $C_{16}H_{16}O_4$ requires $M^+$ 272.1049.

***p*-Methoxybenzyl salicylate** $^1$H NMR ($CDCl_3$) δ 3.8 (3 H, s, $OCH_3$), 5.0 (2 H, s, $CH_2$), 6.8 (2 H, d, *J* 9.8 Hz, Ar-H), 6.9 (2 H, m, Ar-H), 7.2 (2 H, d, *J* 9.8 Hz, Ar-H), 7.5 (1H, t, *J* 7.5 Hz, Ar-H), 7.8 (1 H, d, *J* 7.5 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$) δ 55.20, 65.64, 112.07, 113.80, 116.80, 118.67, 128.00, 130.20, 132.89, 135.20, 158.95, 161.57, 172.85; FAB-MS m/z 258 ($M^+$), 121 ($M^+$-137, 100%); HRMS Found $M^+$ 258.0886; $C_{15}H_{14}O_4$ requires $M^+$ 258.0892.

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