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Efficient Preparation and Processing of the 4-Methoxybenzyl (PMB) Group for Phenolic Protection Using Ultrasound[†,1]

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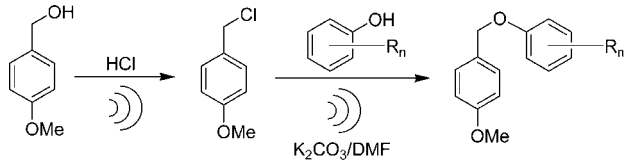
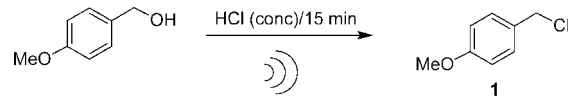


Power ultrasound efficiently facilitates the rapid preparation and reaction of 4-methoxybenzyl chloride (PMB-Cl) **1** in providing protected phenolic ether intermediates for organic synthesis. Using two-phase systems in both the ultrasound-promoted preparation and reactions of PMB-Cl, typical runs produce PMB-protected products within 15 min. When compared with nonsonicated control reactions, the results demonstrate clear advantage in terms of efficiency when the protocol is applied to the mild and selective protection of various multisubstituted phenols including sensitive phenolic aldehydes.

The 4-methoxybenzyl (PMB or MPM) group has been extensively used as a protecting group for alcohols, phenols and various nitrogen moieties in organic synthesis.[2] Some time ago we used the PMB group for the efficient protection of the imide nitrogen in ribosyl nucleobases,[3a] and in the protection of the glutarimide nitrogen in thalidomide analogues.[3b] However, the PMB group has since gained in popularity and is now a "textbook" protecting group as it has been used in applications too numerous to specifically cite here.[3c–e] For most applications overall, such as those in carbohydrate chemistry, the PMB group is more robust and less expensive than many of the silicon-based protecting groups and can be removed by a wide range of reagent systems. Introduction of the PMB group is mainly facilitated with 4-methoxybenzyl chloride (PMB-Cl) **1**, a compound which has safety and stability issues associated with its handling, shipping and storage.[4] Other types of benzylating reagents can take the form of the corresponding benzylic iodide, bromide or trichloroacetimidate, depending on the degree of mildness required by the protection step.[5] More recently, benzylating reagents have taken the form of the corresponding 2-benzyl or 2-(4-methoxybenzyl)pyridinium or -quinolinium triflates.[6] Typically, the preparation of benzylic chlorides such as PMB-Cl or benzyl chloride can be performed under mild, nonaqueous conditions by treatment of the corresponding alcohols with chlorinating reagent systems utilizing thionyl chloride, *N*-chlorosuccinimide, triphenylphosphine/isocyanuric chloride or tertiary halides in ionic liquids.[7] In contrast, conversion of 4-methoxybenzyl alcohol to PMB-Cl **1** may be facilitated more economically by the employment of hydrochloric acid under strictly aqueous conditions or with the use of a cosolvent.[8] Organic reaction processes involving liquid−liquid and solid−liquid systems can be normally facilitated by power ultrasound.[9] Hence, we determined that the two-phase halogenation reaction involving *p*-anisyl alcohol and aqueous concentrated HCl (eq 1) with promotion by ultrasound would be a good case in point and would rapidly provide **1** at minimal expense.



(1)

When power ultrasound was applied to a suspension of reagent-grade concentrated hydrochloric acid and *p*-anisyl alcohol for 15 min, the immediate result was the formation of a top layer of the 4-methoxybenzyl chloride. The product

[†] Dedicated to Professor E. J. Corey on the occasion of his 80th birthday.

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(10) (a) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945. For an array of protected phenols, see:(b) Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A.; Vijaykumar, D. *J. Org. Chem.* **1995**, *60*, 5961–5962. (c) Recently, power ultrasound was employed to protect alcohols as silyl ethers under solvent free conditions: Mojtahedi, M. M.; Abaee, M. S.; Hamidi, H.; Zolfaghari, A. *Ultrason. Sonochem.* **2007**, *14*, 596–598.

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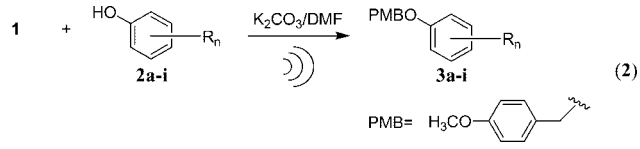
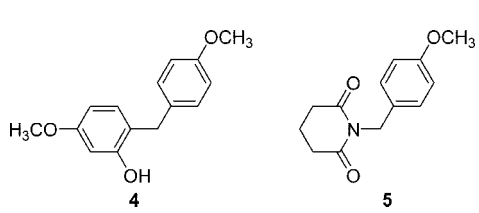
chloride **1** was then easily separated from the aqueous portion and dried, whereupon ^{1}H NMR analysis demonstrated the product to be at least 98% pure. The product could then be used in a subsequent reaction or otherwise Kugelröhr-distilled and then immediately employed in any reaction or protection step. The distilled 4-methoxybenzyl chloride can also be stored for up to three weeks over a small amount of anhydrous powdered potassium carbonate and taken out by syringe as needed. With an efficient method for preparing PMB-Cl now in hand we put it to practice in a separate project which initially involved the rapid preparation of a number of PMB-protected phenolic aldehydes for use in the Henry reaction.[10a] Hence, we were prompted as well to explore the application of power ultrasound in the protection of the phenolic hydroxyl under heterogeneous conditions using the freshly prepared PMB chloride.[10b,c] Potassium bases such as potassium hydroxide or potassium carbonate together with a polar aprotic solvent, typically acetone under reflux, appear to be the reagent systems or conditions of choice when alkylating phenolic oxygens. Since acetone is relatively low boiling, we decided to use *N*,*N*-dimethylformamide (DMF) as the reaction medium due to its similar polarity and significantly higher boiling point, a property which we found compatible with power ultrasound when external cooling was not employed. We also employed reagent-grade anhydrous potassium carbonate to promote the reaction between the substrate phenol and **1** (eq 2). Applying ultrasound



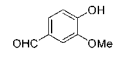
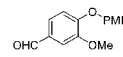
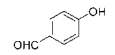
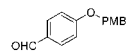
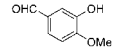
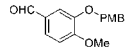
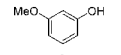
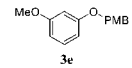
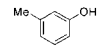
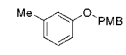
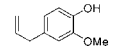
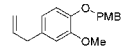
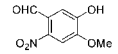
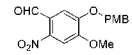
(2)

to a suspension of a typical substrate phenol **2a**−**i** and PMB-Cl (one molar equivalent each) and 2 equiv of potassium carbonate in anhydrous DMF resulted in complete consumption of starting material in 15 min (Table 1). Following extractive workup, concentration and silica gel chromatography, the products **3a**−**i** were isolated in modest to high yields. For comparison, nonsonicated (usually termed stirred or "silent") reactions were conducted with the same group of substrates while monitoring their disappearance by thin-layer chromatography (Table 1). From comparing the reaction times of both the sonicated and nonsonicated control experiments, it is clearly evident that ultrasound offers an expedient in terms of time but not a great advantage in terms of yield. The efficiency advantage is apparent when considering the conversion of simple aldehydic phenols such as **2 h** → **3 h** (15 min sonicated, 97% versus 17 h nonsonicated, 97%). But in contrast, ultrasound compromises the yields in the cases of more activated substrates such as the allyl phenols **2b** and **2g**. In one of the experiments involving **2e** → **3e**, we isolated the phenolic methoxydiphenylmethane **4**(∼6%), which presumably occurs through acid-catalyzed ortho



rearrangement of **3e**. Not surprisingly, similar rearrangements were found to occur during the deprotection of PMB phenolic ethers.[10b] In order to clarify the role of anhydrous potassium carbonate as either a base in generating phenoxide ion or as a simple buffering agent, several control reactions were carried out using deuterium oxide (D_2O). Sonication of a suspension of anhydrous potassium carbonate and *m*-cresol in DMF in the presence of D_2O resulted in no phenolic deuterium exchange while the same experiments employing anhydrous potassium hydroxide instead of K_2CO_3 resulted in complete deuterium exchange.[11] Hence, these results suggest that potassium carbonate acts as an active buffer which absorbs the generated hydrogen chloride and that power ultrasound accelerates the buffering action by formation of a reactive microdispersion of K_2CO_3 in DMF. Moreover, when considering that many protocols require the generation of a preformed phenoxide when preparing benzylic phenolic ethers, the sonication method in DMF represents a simpler and more convenient methodology. For purposes of comparison, benzyl chloride was substituted for PMB-Cl in the sonicated reaction of substrate **2e** with all conditions remaining the same as in Table 1. As expected the less reactive benzyl halide cleanly afforded the benzyl analogue of **3e**, 1-(benzyloxy)-3-methoxybenzene, in 51% conversion after 15 min, thereby suggesting that the sonication avenue may have potential in providing simple Bn-protected phenolic ethers. Preliminary experiments with ultrasound-promoted N-protection

TABLE 1. Ultrasound-Promoted and Silent (Control) Conversions of Phenols to PMB Ethers

Phenol	Product	Ultrasound Yield, %[1, 2, 4]	Control Yield %/Time[2, 3]
 **2a**	 **3a**	83	97/24h
 **2b**	 **3b**	48	91/27h
 **2c**	 **3c**	95	91/20h
 **2d**	 **3d**	89	95/23h
 **2e**	 **3e**	90	92/24h
 **2f**	 **3f**	90	89/24h
 **2g**	 **3g**	77	97/25h
 **2h**	 **3h**	97	97/17h
 **2i**	 **3i**	43	26/24h

[1] Reactions were run for **15 min** with a 300 W Sonics and Materials Vibra-Cell titanium probe. [2] Yields are for isolated, purified product. [3] The reaction times listed are for full disappearance of starting material as determined by analytical TLC unless otherwise noted. [4] New compounds (**3e**−**3i**) were characterized by ^{1}H, ^{13}C NMR, IR and HRMS.

(11) Acetone as a solvent, which is less polar (μ, 2.69) and has a lower dielectric constant (ε, 20.70), gave no deuterium exchange with K_2CO_3, *m*-cresol and ultrasound.

of imides with **1** were promising. Treatment of a suspension of glutarimide, **1** and K_2CO_3/DMF with ultrasound irradiation (20min) gave *N*-PMB glutarimide **5** in 86% recrystallized yield while the nonsonicated control reaction required 24 h for complete conversion to **5** (Supporting Information).[12] The growing number of laboratories having access to microwave equipment as compared to those using power ultrasound equipment prompted us to conduct experiments with microwaves for comparison. Admixture of *p*-anisyl alcohol to concentrated HCl followed by irradiating the suspension with microwaves (30min/120 °C) gave **1** in 71% yield after workup and bulb-to-bulb (Kugelröhr) distillation. Furthermore, microwave irradiation efficiently promoted the preparation of the O-PMB aldehyde **3c** (94%) using freshly prepared **1** and phenolic aldehyde **2c**.[13]

In summary, power ultrasound efficiently facilitates the rapid conversion of *p*-anisyl alcohol to PMB-Cl using hydrochloric acid and thus avoids the use of more expensive chlorinating reagents and lengthy workup and purification procedures. The PMB-Cl thus prepared can be stored over potassium carbonate for extended periods; however, it is best used immediately after separation from the reaction mixture or after bulb-to-bulb distillation. In terms of expense, convenience and time the rapid preparation and use of PMB-Cl far precludes purchase and storage of the material. Using ultrasound in sequence, the freshly prepared PMB chloride was used to protect an array of phenolic hydroxyl groups rapidly and in good yield while again avoiding prolonged reaction times and low-boiling refluxing solvent systems. Moreover, the method is an efficient alternative to the time-consuming preparation and use of the corresponding phenoxides prior to treatment with **1**. The application of the ultrasound method to the preparation of protected phenolic aldehydes has been especially useful as these intermediates are available quickly and react smoothly in a variety of carbon−carbon bond-forming transformations.

Experimental Section

4-Methoxybenzyl Chloride (PMB-Cl or MPM Chloride (1). In a 500 mL round-bottom flask was placed *p*-anisyl alcohol (20 mL, 22.24 g, 161.12 mmol) followed by concentrated HCl (160 mL). Upon addition of the acid, the heterogeneous mixture then turned cloudy white. The ultrasound probe (1/4″ microtip) was immersed 0.5″ below the surface, and the instrument was turned to full power. The reaction mixture then turned homogeneous during the sonication process. After 15 min, the reaction mixture was poured into a separatory funnel, and the top chloride layer was separated and dried over anhydrous calcium chloride. Removal of the drying agent gave product (19.1 g, 75%) of sufficient purity to use directly in many of the reactions. Kugelröhr distillation (117−118 °C @ 1 mm)[8a] gave the product chloride **1** of excellent purity which can be stabilized by addition of powdered anhydrous potassium carbonate and stored under nitrogen.

General Procedure for the Preparation of Phenolic PMB Ethers (3a−i). In a 100 mL round-bottom flask was placed potassium carbonate (6 mmol, 2 equiv) and the substrate phenol **2a−i** (3 mmol, 1 equiv) followed by *N*,*N*-dimethylformamide (6−6.5 mL) and 4-methoxybenzyl chloride **1** (3 mmol, 1 equiv). The ultrasound probe (1/4″ microtip) was immersed 0.5″ below the surface, and the instrument was turned to full power. After 15 min, the reaction mixture was diluted with distilled H_2O (200 mL) and poured into a separatory funnel. The product was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were dried over magnesium sulfate and concentrated. The crude residue was purified by gravity column chromatography (hexane/ethyl acetate) on silica gel to afford the PMB phenolic ether products **3a−i**.

4-(4-Methoxybenzyloxy)-3-methoxybenzaldehyde (3a): white solid (mp 105−106 °C, Lit.[14] 106−107 °C), R_f 0.45 (hexane/ethyl acetate, 1:1).

1-(4-Methoxybenzyloxy)-2-allylbenzene (3b): colorless oil (Lit.[15]), R_f 0.50 (hexane/ethyl acetate, 4:1).

4-(4-Methoxybenzyloxy)benzaldehyde (3c): white solid (mp 100−101 °C, Lit.[16] 101−102 °C), R_f 0.52 (hexane/ethyl acetate, 1:1).

3-(4-Methoxybenzyloxy)-4-methoxybenzaldehyde (3d): white solid (mp 79−80 °C, Lit.[14] 80−81 °C), R_f 0.40 (hexane/ethyl acetate, 1:1).

1-Methoxy-3-(4-methoxybenzyloxy)benzene (3e): white solid (mp 41−42 °C), R_f 0.35 (hexane/ethyl acetate, 4:1); FTIR (KBr, cm^{-1}) 3054, 2986, 1604, 1515, 1422, 1264, 1151, 1035, 895, 738, 706. ^{1}H NMR (500 Hz, $CDCl_3$) δ 3.79 (s, 3H), 3.83 (s, 3H), 4.98 (s, 2H), 6.54 (d, 2H), 6.59 (d, 1H), 6.93 (d, 2H), 7.19 (t, 1H), 7.37 (d, 2H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 160.8, 160.1, 159.4, 129.8, 129.2, 129.0, 114.0, 106.9, 106.5, 101.3, 69.8, 55.3, 55.2; HRMS ($[M + H]^+$) calculated for $C_{15}H_{16}O_3$ ($[M + Na]^+$) 245.1172, found 245.1174.

1-(4-Methoxybenzyloxy)-3-methylbenzene (3f): white solid (mp 60−61 °C), R_f 0.52 (hexane/ethyl acetate, 4:1); FTIR (KBr, cm^{-1}) 3054, 2986, 1612, 1515, 1421, 1265, 737, 706. ^{1}H NMR (500 Hz, $CDCl_3$) δ 2.38 (s, 3H), 3.86 (s, 3H), 5.01 (s, 2H), 6.82 (d, 2H), 6.86 (d, 1H), 6.96 (d, 2H), 7.21(t, 1H), 7.40 (d, 2H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 159.4, 158.9, 139.5, 129.2, 121.7, 115.7, 113.9, 111.6, 69.6, 55.2, 21.5; HRMS ($[M + H]^+$) calculated for $C_{15}H_{16}O_2$ ($[M + H]^+$) 229.1228, found 229.1226.

4-Allyl-2-methoxy-1-(4-methoxybenzyloxy)benzene (3 g): white solid (mp 85−86 °C), R_f 0.33 (hexane/ethyl acetate, 4:1); FTIR (KBr, cm^{-1}) 3853, 3735, 3054, 2986, 1516, 1397, 1265, 737, 706. ^{1}H NMR (500 Hz, $CDCl_3$) δ 3.35 (d, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 5.07 (s, 2H), 5.10 (m, 2H), 5.97 (m, 1H), 6.68 (dd, 1H), 6.75 (d, 1H), 6.85 (d, 1H), 6.91 (d, 2H), 7.38 (d, 2H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 159.2, 149.6, 146.5, 137.6, 133.2, 129.3, 128.9, 120.3, 115.6, 114.4, 113.8, 112.4, 70.9, 55.9, 55.2, 39.8; HRMS ($[M + Na]^+$) calculated for $C_{18}H_{20}O_3$ ($[M + Na]^+$) 307.1309, found 307.1306.

2-(4-Methoxybenzyloxy)benzaldehyde (3 h): yellow solid (mp 88−89 °C), R_f 0.30 (hexane/ethyl acetate, 4:1); FTIR (KBr, cm^{-1}) 3853, 3749, 3688, 1684, 1597, 1516, 1456, 1251, 1187, 1026, 828, 737,706. ^{1}H NMR (500 Hz, $CDCl_3$) δ 3.82 (s, 3H), 5.12 (s, 2H), 6.94 (d, 2H), 7.05 (q, 2H), 7.37 (d, 2H), 7.54 (t, 1H), 7.85 (d, 1H), 10.52 (s, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 189.9, 161.1, 159.6, 135.9, 129.1, 128.4, 128.0, 125.2, 120.9, 114.1, 113.1, 70.3, 55.3; HRMS ($[M + Na]^+$) calculated for $C_{18}H_{20}O_3$ M + $Na]^+$) 265.0840, found 265.0837.

4-Methoxy-5-(4-methoxybenzyloxy)-2-nitrobenzaldehyde (3i): yellow solid (mp 109−110 °C), R_f 0.20 (toluene/ethyl acetate, 99:1); FTIR (KBr, cm^{-1}) 3944, 3757, 3690, 3055, 2986, 2839, 2685, 1689, 1572, 1518, 1422, 1265, 1175, 1060, 895, 737,706. ^{1}H NMR (500 Hz, $CDCl_3$) δ 3.82 (s, 3H), 4.02 (s, 3H), 5.21 (s, 2H), 6.93 (d, 2H), 7.39 (d, 2H), 7.50 (s, 1H), 7.62 (s, 1H), 10.44 (s, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 187.7, 159.9, 152.8, 152.4, 143.8, 129.5, 128.9, 128.5, 127.0, 125.3, 114.2, 111.3, 107.3, 71.2, 56.7, 55.3; HRMS ($[M + Na]^+$) calculated for $C_{16}H_{15}NO_6$ ($[M + Na]^+$) 340.0796, found 340.0793.

Preparation of 4-Methoxybenzyl Chloride (PMB-Cl or MPM chloride) (1) by Microwave Irradiation. *p*-Anisyl alcohol

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(1 mL, 1.11 g, 8.05 mmol) was placed in a 10 mL reaction tube followed by concentrated HCl (2 mL). Upon addition of the acid, the heterogeneous mixture then turned cloudy white. The tube was sealed, placed into the microwave apparatus and irradiated (30 min/120 °C). After irradiation, the reaction mixture was poured into a separatory funnel, and the top chloride layer was separated and dried over anhydrous calcium chloride. Removal of the drying agent and Kugelrohr distillation (as above) gave the product chloride **1** (0.91 g, 71%) of excellent purity which can be stabilized by addition of powdered anhydrous K_2CO_3.

Preparation of 4-(4-Methoxybenzyloxy) benzaldehyde (3c) by Microwave Irradiation. 4-Hydroxybenzaldehyde **2c** (0.09 g, 0.74 mmol), potassium carbonate (0.20 g, 1.48 mmol, 2 equiv) and *N*,*N*-dimethylformamide (1 mL) were placed in a 10 mL reaction tube followed by 4-methoxybenzyl chloride **1** (0.10 mL, 0.74 mmol, 1 equiv). The tube was sealed and placed into the microwave apparatus and irradiated (30 min/120 °C). After irradiation, the reaction mixture was diluted with distilled H_2O (30 mL) and poured into a separatory funnel. The product was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over magnesium sulfate and concentrated. The crude residue was purified by gravity column chromatography on silica gel (hexane/ethylacetate, 1:1) to afford the PMB-protected aldehyde product **3c** which gave analytical data identical to those of the product of the corresponding ultrasound experiment.

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Supporting Information Available: Experimental procedures for the sonicated and nonsonicated (control) preparation of **5**; ^1H and ^{13}C NMR spectra of all new compounds **(3e−i)**. This material is available free of charge via the Internet at http://pubs.acs.org.

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