Synthesis of *para*-methoxybenzyl (PMB) ethers under neutral conditions

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2-(4-Methoxybenzyloxy)-4-methylquinoline reacts with methyl triflate in the presence of alcohols to generate a neutral organic salt that transfers the *para*-methoxybenzyl (PMB) protecting group onto alcohols in high yield and under mild conditions.

para-Methoxybenzyl (PMB) ethers are workhorse protecting groups in organic synthesis.[1] Like benzyl (Bn) ethers, PMB ethers withstand a wide range of reaction conditions, can be cleaved under mild conditions,[2] and are not subject to the unwanted migration between neighboring functional groups that is observed with ester, acetal, and silyl ether protecting groups. However, the formation of PMB ethers can be problematic. Common methods for the synthesis of PMB ethers—Williamson[3] and trichloroacetimidate[4] coupling reactions—require basic or acidic media that may not be compatible with complex systems.[5] Furthermore, neither PMB trichloroacetimidate (unstable to storage) nor PMB chloride (lachrymator) is especially convenient for routine usage.

We recently introduced *2-benzyloxy-1-methylpyridinium triflate* (***4***),[6] a stable organic salt that provides benzyl ethers upon warming in the presence of alcohols (Eq. 1).[7] An analogous synthesis of the more versatile PMB ethers would be widely applicable in synthetic chemistry.[8] PMB salt **7** (Fig. 1) is reactive at room temperature in methylene chloride, but it is not soluble in the aromatic solvents (trifluorotoluene or toluene) that we found to be optimal for reaction efficiency. We therefore targeted a more hydrophobic reagent (*i.e.*, lepidine salt **8**) and prepared 2-(4-methoxybenzyloxy)-4-methylquinoline (**1**, Eq. 2).†

(1)

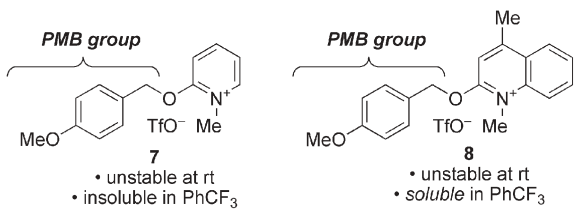

Fig. 1 PMB transfer salts.

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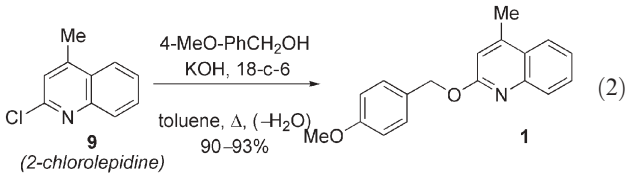
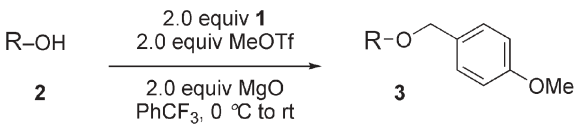


(2)

Preliminary experiments showed that lepidine derivative **8** is soluble in aromatic solvents: addition of methyl triflate (MeOTf) to lepidine ether **1** in trifluorotoluene[9] did *not* produce a visible precipitate despite rapid consumption of **1** with concomitant formation of polar material.[10] Lepidine ether **1** is significantly more stable than other PMB transfer reagents such as PMB chloride[3] and PMB trichloroacetimidate.[4] Furthermore, *addition of methyl triflate to mixtures containing alcohols **2** and lepidine **1** affords PMB ethers **3*** (Table 1).‡

As shown in Table 1, the formation of PMB ethers using **1** and methyl triflate occurs efficiently on a range of alcohols (depicted in Fig. 2). The presence of magnesium oxide (MgO) provides for higher yields and easier purification of **3**. *N*-Methyl-lepidone (**10**) is the expected by-product of this reaction; bis-PMB ether **11**, presumably derived from adventitious moisture and/or reaction with magnesium oxide, is also observed in varying amounts.

Table 1 Arylmethylation of representative alcohols (**2** → **3**, see Fig. 2)[a]



Entry	Alcohol **2**	Ether **3**	% yield[b]
1	**2a**	**3a**	94
2	**2b**	**3b**	98
3	**2c**	**3c**	63[c]
4	**2d**	**3d**	90
5	**2e**	**3e**	89
6	**2e**	**3e**	69[d]
7	**2f**	**3f**	60[c]
8	**2g**	**3g**	84
9	**2h**	**3h**	99
10	**2i**	**3i**	80[c]
11	**2i**	**3i**	98[e]

[a] Unless otherwise indicated, methyl triflate was added to a mixture of alcohol **2**, lepidine **1**, MgO, and trifluorotoluene under argon. [b] Isolated yield. [c] Alcohol **2** was not fully consumed after 1 h. [d] Potassium carbonate (K_2CO_3) employed in lieu of MgO. [e] Toluene employed in lieu of $PhCF_3$.

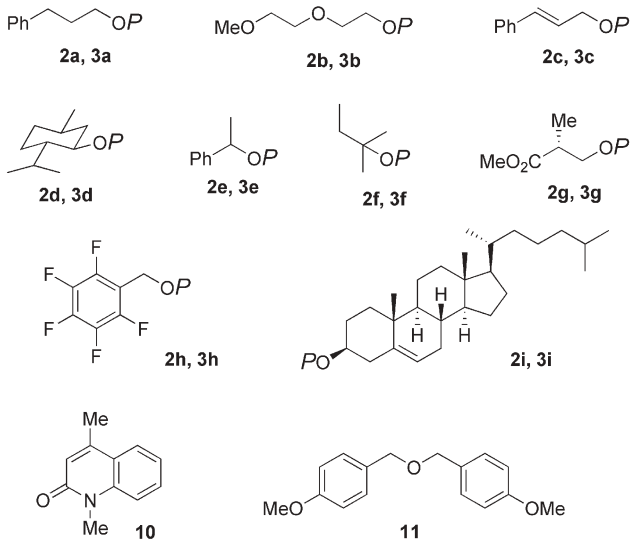
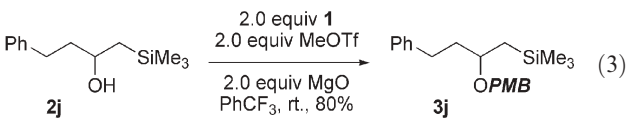


Fig. 2 Substrates and products from the arylmethylation reactions listed in Table 1. For **2a–i**, P = H. For **3a–i**, P = PMB.

Other aromatic solvents (*e.g.*, toluene, entry 11) and heterogeneous acid scavengers (*e.g.*, potassium carbonate, entry 6) may be employed in lieu of trifluorotoluene and magnesium oxide. Simple primary and secondary alcohols (entries 1–6) gave rise to the corresponding PMB ethers (**3a–e**) generally in good to excellent yield. Allylic alcohol **2c** was not fully consumed for some reason (entry 3), whereas benzylic alcohols **2e** and **2h** proved to be good substrates (entries 5 and 9). Tertiary alcohols (*e.g.*, **2f**, entry 7) were less reactive. PMB-protection of cholesterol (**2i** → **3i**, entry 10) proceeded reasonably under the standard conditions (80%) despite limited solubility of **2i** in trifluorotoluene. The same reaction in toluene afforded **3i** in nearly quantitative yield (entry 11). The Roche ester (**2g**) gave rise to PMB ether **3g** in 84% yield (entry 8).



(3)

The etherification of alcohol **2j** (Eq. 3) illustrates the tolerance of the reaction conditions to sensitive functionality. Alcohol **2j** is subject to Peterson elimination[11] under acidic or basic conditions, but transfer of the PMB-group provides ether **3j** with no evidence of the potential elimination by-product, 4-phenyl-1-butene.

In keeping with our earlier work on the synthesis of benzyl ethers,[6] we propose that the current synthesis of PMB ethers proceeds by an S_N1-type mechanism analogous to that observed from trichloroacetimidates. Critical to the success of our approach is that the neutral alcohol (**2**) does not react with methyl triflate,[12] whereas alcohol **2** *does* react with the *p*-methoxybenzyl cation as it is released from active reagent **8**.

Lepidine ether ***1*** *provides several key advantages over PMB trichloroacetimidate*: (1) ether **1** is more stable; (2) active reagent **8** is generated under non-acidic conditions; and (3) the by-product, lepidone **10**, remains in solution until it is purged either during aqueous workup or on silica gel chromatography. In contrast, the acetamide by-product of trichloroacetimidate coupling reactions can cause problems during purification.

In summary, we report a new *p*-methoxybenzyloxy derivative of lepidine that, upon treatment with methyl triflate, transfers the PMB group to an awaiting alcohol substrate. Methylation of the lepidine core generates an activated reagent under effectively neutral conditions, allowing acid- and base-sensitive alcohols (*e.g.*, **2j**) to be protected as PMB ethers. We expect this protocol to be of considerable utility.

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Notes and references

† **2-(4-Methoxybenzyloxy)-4-methylquinoline (1)** A mixture of 4-methoxybenzyl alcohol (3.6 g, 26 mmol), 2-chlorolepidine (3.6 g, 21 mmol), KOH (4.8 g, 86 mmol, ground with a mortar and pestle), toluene (41 mL) and 18-crown-6 (318 mg, 1.2 mmol) was heated at reflux for 1 h with azeotropic removal of water (Dean–Stark trap). The reaction mixture was then cooled to room temperature and partitioned between ethyl acetate (100 mL) and water (50 mL). The organics were washed (brine), dried ($MgSO_4$), filtered, concentrated under vacuum, and purified on silica gel (elution with 5% EtOAc–hexanes) to provide 5.3 g of **1** (93% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (br d, J = 8.4 Hz, 2H), 7.62 (td, J = 7.6, 1.3 Hz, 1H), 7.49–7.37 (m, 3H), 6.92 (d, J = 6.7 Hz, 2H), 6.79 (s, 1H), 5.46 (s, 2H), 3.82 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 159.7, 147.0, 146.8, 130.3, 129.8, 129.5, 128.0, 125.8, 124.0, 123.9, 114.1, 113.5, 67.4, 55.5, 18.9. IR 1611, 1573, 1514, 1470, 1448, 1396, 1329, 1303, 1246, 1174, 1130, 1039, 1020 cm^{-1}. HRMS (ESI$^+$) found 302.1163 (calcd for $C_{18}H_{17}NO_2Na$: 302.1157).

‡ **Standard procedure for the arylmethylation of alcohols (2 → 3)** An ice-cold mixture of 2-PMBO-lepidine **1** (200 mg, 0.72 mmol), benzotrifluoride ($PhCF_3$, 3.6 mL), MgO (29 mg, 0.72 mmol, vacuum-dried), and alcohol **2** (0.36 mmol) was treated dropwise with methyl triflate (82 μL, 0.72 mmol). The ice bath was removed, and the reaction mixture was stirred at room temperature for 30–60 min until TLC analysis showed consumption of alcohol **2**. The mixture was then diluted with ethyl acetate, decanted away from the MgO residue, washed (H_2O), dried ($MgSO_4$), filtered, concentrated at reduced pressure, and purified on silica gel to yield PMB ether **3** (see Table 1).

1 (*a*) T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley and Sons, New York, 3rd edn, 1999; (*b*) P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, 3rd edn, 2003.
2 Y. Oikawa, T. Yoshioka and O. Yonemitsu, *Tetrahedron Lett.*, 1982, **23**, 885.
3 P. G. M. Wuts, *p*-Methoxybenzyl Chloride, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, John Wiley and Sons, New York, 1995, Vol. 5, p. 3326.
4 (*a*) P. G. M. Wuts, 4-Methoxybenzyl 2,2,2-Trichloroacetimidate, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, John Wiley and Sons, New York, 1995, Vol. 5, p. 3329; (*b*) Attractive method for the synthesis of PMB ethers using catalytic lanthanum triflate: A. N. Rai and A. Basu, *Tetrahedron Lett.*, 2003, **44**, 2267.
5 *The Chemical Synthesis of Natural Products*, ed. K. Hale, CRC Press, Boca Raton, Florida, 2000.
6 (*a*) K. W. C. Poon and G. B. Dudley, *J. Org. Chem.*, 2006, **71**, 3923; (*b*) K. W. C. Poon, S. E. House and G. B. Dudley, *Synlett*, 2005, 3142; (*c*) G. B. Dudley, US Pat. Appl. No. 11/399,300, 2006.
7 Benzyloxy salt **4** is commercially available from Sigma-Aldrich Chemical Co. (catalog # 679674-1g, 679674-5g).
8 Typical reagents for the formation of PMB ethers are more reactive and less stable than reagents for the synthesis of benzyl ethers; see P. J. Kocienski, *Protecting Groups*, Thieme, Stuttgart, 3rd edn, 2003, p. 257.
9 Trifluorotoluene, also known as benzotrifluoride or BTF, is often used industrially as an alternative to dichloromethane.
10 An analogous modification of Mukaiyama's reagent improved its solubility in non-polar solvents; see: S. H. Oh, G. S. Cortez and D. Romo, *J. Org. Chem.*, 2005, **70**, 2835.
11 D. J. Ager, *Org. React.*, 1990, **38**, 1.
12 Methyl tosylate, dimethyl sulfate and methyl iodide were not effective substitutes for methyl triflate.