A New, Convenient Reductive Procedure for the Deprotection of 4-Methoxybenzyl (MPM) Ethers to Alcohols

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Selective introduction and removal of protecting groups is of great significance in organic synthesis.[1] The benzyl ether function is one of the most common protecting groups for alcohols. Selective oxidative removal of the 4-methoxybenzyl (MPM) ethers in the presence of benzyl ethers made the MPM moiety an alternative protecting group, and its utility in carbohydrate chemistry is well established. Several procedures have been developed for the cleavage of the 4-methoxybenzyl moiety, e.g. DDQ oxidation (eq 1),[2] electrochemical oxidation,[3] homogeneous electron transfer,[4] photoinduced single electron transfer,[5] boron trichloride–dimethyl sulfide,[6] etc. However, in all these methods isolation of the alcohol from the inevitable byproduct, 4-methoxybenzaldehyde [also dichlorodicyanohydroquinone (DDHQ) in the most commonly used method employing DDQ] can be troublesome. Recently Wallace and Hedgetts[7] discovered that acetic acid at 90 °C cleaves the aromatic MPM ethers into the corresponding phenols and 4-methoxybenzyl acetate (eq 2), whereas the aliphatic MPM ethers generated, instead of alcohols, the corresponding acetates (eq 3). Complimentary to this methodology, herein we report that sodium cyanoborohydride and boron trifluoride etherate reductively cleaves, cleanly and efficiently, the aliphatic MPM ethers to an easily separable mixture of the corresponding alcohols and 4-methylanisole (eq 4).

$$\text{ROMPM} + \text{DDQ} \rightarrow \text{ROH} + \text{DDHQ} + \text{1,4-MeO-C}_6\text{H}_4\text{CHO} \quad \text{(eq 1)}$$

$$\text{ArO-MPM} + \text{AcOH} \rightarrow \text{ArOH} + \text{MPM-OAc} \quad \text{(eq 2)}$$

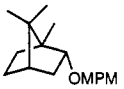
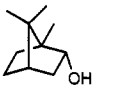
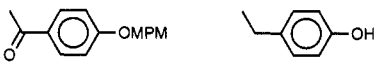
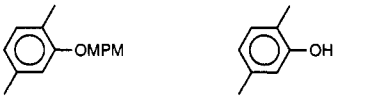
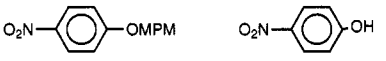
$$\text{RO-MPM} + \text{AcOH} \rightarrow \text{ROAc} + \text{MPM-OAc} \quad \text{(eq 3)}$$

$$\text{RO-MPM} + \text{NaCNBH}_3 + \text{BF}_3\cdot\text{OEt}_2 \rightarrow \text{ROH} + \text{1,4-MeO-C}_6\text{H}_4\text{Me} \quad \text{(eq 4)}$$

(MPM = (4-methoxyphenyl)methyl)

Thus treatment of *n*-undecyl MPM ether with boron trifluoride etherate and sodium cyanoborohydride in refluxing THF for 8 h furnished a mixture of *n*-undecanol and 4-methylanisole in almost quantitative yield, which was easily separated by a small silica gel column. In contrast, reaction in the absence of sodium cyanoborohydride gave a mixture of several products including unreacted starting material and *n*-undecanol. To test the generality of this methodology, MPM ethers[3,5] of various primary and secondary alcohols and phenols were prepared using the standard procedure and subjected to the reductive cleavage with sodium cyanoborohydride and boron trifluoride etherate in refluxing THF. The results are summarized in Table 1. The reductive cleavage was found to be very clean with aliphatic MPM ethers. Most importantly the benzyl ethers of both aliphatic alcohol as well as that of phenol were found to be stable under these conditions (entries 5 and 12). Quite expectedly[8a] in entry 9, in addition to the reductive cleavage of MPM ether, the aryl ketone was also deoxygenated. In contrast to the aliphatic ethers, reaction with the aromatic MPM ethers, in particular those derived from electron rich phenols (entries 10 and 11), gave considerable amounts of rearrangement products (C–C coupled products);[9] (4-methoxyphenyl)methyl substituted phenols were also obtained.[10] The reduction of the nitro group was found to be competing under these conditions and quite inter-

Table 1. Reductive Cleavage of MPM Ethers

entry	ether	ROH	time, h	yield,[a] %
1	*n*-$C_{11}H_{23}$O-MPM	*n*-$C_{11}H_{23}$OH	10	98
2	*n*-$C_{12}H_{25}$O-MPM	*n*-$C_{12}H_{25}$OH	10	94
3	$Me_2CH(CH_2)_7O$-MPM	$Me_2CH(CH_2)_7OH$	10	86
4	$Me_2CH(CH_2)_5O$-MPM	$Me_2CH(CH_2)_5OH$	10	83
5	*n*-$C_{12}H_{25}OCH_2Ph$	–	24[b]	–
6	cholesteryl-O-MPM	cholesterol	6	94
7	cyclododecyl-O-MPM	cyclododecanol	12	86
8			12	85
9			5	70[c]
10			8	65[d]
11			6	65[e]
12		–	24[b]	–
13			4[f]	70
14		–	10[b]	–

[a] Yields (unoptimized) refer to isolated and chromatographically pure products. The products were identified by comparison (TLC, IR, NMR) with authentic samples. [b] Only starting material was recovered. [c] In addition ca. 7% of rearranged product was also formed. [d] In addition ca. 30% of rearranged products were also formed. [e] In addition ca. 25% of rearranged products were also formed (see text). [f] No $NaCNBH_3$ was used.

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(10) With β-naphthyl MPM ether only rearrangement product was observed.

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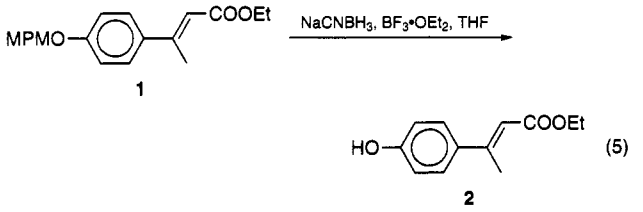
estingly 4-nitrophenyl MPM ether (entry 13) cleaved with only boron trifluoride etherate in the absence of sodium cyanoborohydride. The presence of amines or amides (entry 14) was found to inhibit the reaction obviously due to the complexation of boron trifluoride with nitrogen. Finally to establish the versatility of the method the cinnamate **1**,[11] obtained by Wittig–Horner–Emmons reaction on MPM ether of 4-hydroxyacetophenone,[11] was subjected to the reductive cleavage (eq 5). Needless to mention that with the corresponding benzyl ether, removal of benzyl moiety under usual reductive conditions is not possible without affecting the cinnamate moiety. Thus treatment of cinnamate **1** with 2 equiv of sodium cyanoborohydride and boron trifluoride etherate in refluxing THF for 5 h furnished the corresponding phenol **2**,[11] in 77% yield without affecting the cinnamate moiety.



(5)

In conclusion, we have discovered a new reductive methodology for the cleavage of MPM protecting group with an easily separable byproduct, employing sodium cyanoborohydride and boron trifluoride etherate. The stability of esters, in particular cinnamates and most importantly the benzyl ethers, points to the versatility of the methodology.

Experimental Section

Melting points are uncorrected. 4-Methoxybenzyl bromide was prepared from 4-methylanisole and NBS in the presence of AIBN in refluxing CCl_4. 4-Methoxybenzyl ethers were prepared using the standard procedures, employing freshly prepared 4-methoxybenzyl bromide and either NaH in THF at room temperature (for alcohols) or K_2CO_3 in refluxing acetone (for phenols). Boron trifluoride etherate was obtained from E. Merck, and sodium cyanoborohydride was obtained from Fluka and were used without further purification. The identity of the alcohols were established by comparison (TLC, IR, and NMR) with authentic samples.

General Procedure for the Reductive Cleavage of MPM Ethers by Boron Trifluoride Etherate and Sodium Cyanoborohydride. Sodium cyanoborohydride (125 mg, 2 mmol) was added to a magnetically stirred solution of *n*-undecyl MPM ether (300 mg, 1.03 mmol) and boron trifluoride etherate (0.13 mL, 1 mmol) in dry THF (2 mL), and the reaction mixture was refluxed. After 3 h, an additional amount of boron trifluoride etherate (0.13 mL, 1 mmol) was added to the reaction mixture and refluxed for 7 h more (monitored by TLC). The reaction mixture was cooled, diluted with ether (8 mL), and washed with aqueous $NaHCO_3$ followed by brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was charged on a silica gel (*ca.* 8 g) column. Elution of the column with hexanes furnished the 4-methylanisole (116 mg, 95%). Further elution of the column with ethyl acetate–hexane (1:10) furnished *n*-undecanol (174 mg, 98%) which was identified by comparison (TLC, IR, ^1H NMR) with an authentic sample.

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(11) Selected spectral data for 4-(4-methoxybenzyloxy)acetophenone: mp 122–124 °C (3:1 hexane–methylene chloride). IR (Nujol): ν_{max} 1680, 1600, 1520, 1360, 1300, 1250, 1170, 1035, 1000, 830, 815 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.93 and 7.0 (4 H, 2 × AB q, J = 8.9 Hz), 7.36 and 6.92 (4 H, 2 × AB q, J = 8.7 Hz), 5.06 (2 H, s, $ArCH_2O$), 3.82 (3 H, s, OCH_3), 2.56 (3 H, s, $CH_3C{=}O$). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.78; H, 6.35. For ethyl (*E*)-3-[4-(4-methoxybenzyloxy)phenyl]-3-methylbut-2-enoate (**1**): mp 74–76 °C (3:1 hexane–methylene chloride). IR (Nujol): ν_{max} 1710, 1620, 1600, 1510, 1270, 1250, 1160, 1030, 1005, 830, 810, 750 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 7.45 and 6.96 (4 H, 2 × AB q, J = 8.9 Hz), 7.36 and 6.92 (4 H, 2 × AB q, J = 8.7 Hz), 6.11 (1 H, s, olefinic), 5.01 (2 H, s, $ArCH_2O$), 4.21 (2 H, q, J = 7.1 Hz, OCH_2CH_3), 3.82 (3 H, s, OCH_3), 2.56 (3 H, d, J = 0.9 Hz, olefinic CH_3), 1.32 (3 H, t, J = 7.1 Hz, OCH_2CH_3). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.62; H, 6.79. Found: C, 73.69; H, 7.03. For Ethyl (*E*)-3-(4-hydroxyphenyl)-3-methylbut-2-enoate (**2**): mp 90–91 °C (2:1 hexane–methylene chloride). IR (Nujol): ν_{max} 3350 (OH), 1685, 1595, 1510, 1370, 1270, 1215, 1170, 835 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 7.4 and 6.83 (4 H, 2 × AB q, J = 8.9 Hz, aromatic), 6.1 (1 H, q, J = 1.2 Hz, olefinic), 5.48 (1 H, brs, OH), 4.16 (2 H, q, J = 7.2 Hz, OCH_2CH_3), 2.55 (3 H, d, J = 1.2 Hz, olefinic CH_3), 1.31 (3 H, t, J = 7.2 Hz, OCH_2CH_3). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.73; H, 6.81%.