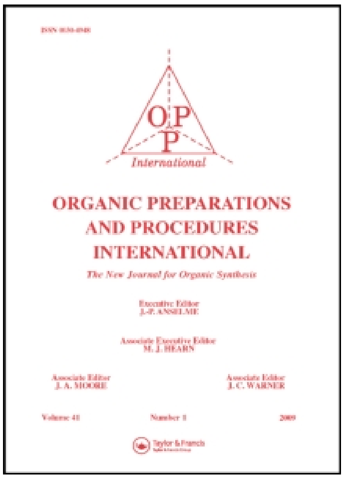

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ZEOLITE-MEDIATED CONVERSION OF ALCOHOLS TO *p*-METHOXYBENZYL ETHERS[†]

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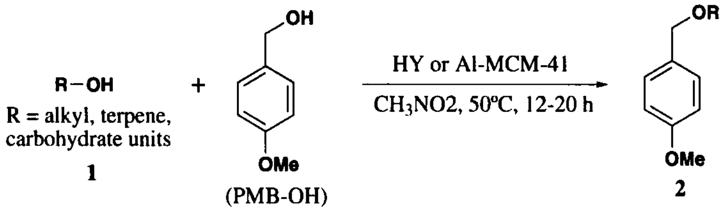
The protection of functional groups[1] is very important for the successful synthesis of complex molecules. The *p*-methoxybenzyl (PMB) and 3,4-dimethoxybenzyl (DMB) groups have proven their usefulness for the protection of hydroxy groups because of the ease with which they can be removed under neutral and mild conditions [2,3-dichloro-5,6 dicyano-benzo-1,4-quinone (DDQ) in aqueous dichloromethane[2] or DDQ-Mn(OAc)$_3$[3]-CH_2Cl_2]. Like the benzyl ether group, the PMB-group is traditionally introduced under basic conditions[4] (NaH, dimethylformamide) or under protic or lewis acidic conditions[5] (BF_3•Et_2O, pyridinium toluene-*p*-sulfonate, trifluoromethanesulfonic acid, camphorsulfonic acid) and with other reagents such as 4-methoxybenzyl-2-pyridylthiocarbonate etc.[6,7] Our recent studies[8] on protection-deprotection resulted in the development of Yb(OTf)$_3$ as a catalyst for the conversion of alcohols into *p*-methoxybenzyl (PMB) ethers.[8b]

Many of the known methods for the protection of alcohols[1] using homogeneous catalysts have certain limitations such as catalyst separation and regeneration, salt formation due to neutralization in the work-up procedure and cost. To overcome these drawbacks, heterogeneous solid acid/base catalysts can contribute tremendously due to eco-friendly conditions with concomitant minimal purification requirements. Our earlier work on the use of solid acids[9] led us to use zeolites[10] for the conversion of alcohols into PMB ethers using PMB alcohol. Zeolites are crystalline aluminosilicates with well-defined geometry and have attracted attention because of their characteristic features such as shape selectivity, thermal stability, reusability and uniquely varying acidic and basic properties.[11] The physical characteristics of the zeolites used are given in *Table 1*. The protonated form of synthetic faujasite zeolite (HY) is a microporous material with three dimensional channel system (available from PQ Corporation, USA). The aluminum form of Mesoporous Composites Material (Al-MCM-41) was synthesized in our laboratory by a method described earlier.[12] It has unidimensional channel system with pore size of 30 Å. The acidity of HY and Al-MCM-41 were measured by NH_3-TPD (stepwise thermal desorption of ammonia) measurements and the surface areas were measured using all glass high vacuum unit by the BET method.[13] Herein, we report a new and efficient protocol for the conversion of alcohols into *p*-methoxybenzyl ethers using these solid acid zeolites.

Table 1. Physical Characteristics of Zeolite Catalysts

Catalyst	Si/Al ratio	Acidity (mmol gm^{-1})	Surface Area ($m^2\ g^{-1}$)	Pore Size (Å)
HY	2.6	2.83	457.2	7.4
Al-MCM-41	15.5	0.319	991.0	30

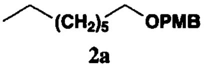
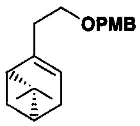
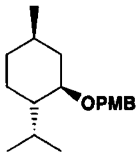
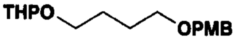
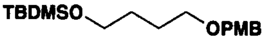
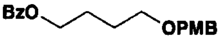
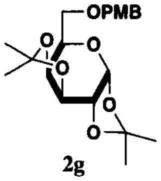
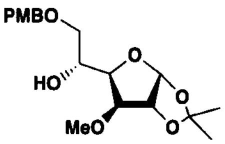
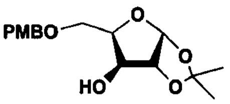
Reaction of octanol (**1a**; 1.0 mmol) with *p*-methoxybenzyl alcohol (PMBOH, 1.0 mmol) and HY zeolite (0.100 g) in $(CH_2)_2Cl_2$ at 50°C gave **2a** in only 20% yield after several hours. However, the same reaction in CH_3NO_2 at 50°C for 12 h gave the product in 56% yield (*Table 1*) along with 20% of corresponding *bis*-(*p*-methoxybenzyl) ether. The catalyst was removed by simple filtration, while the pure product was obtained by chromatographic purification. Similar reaction of **1a** and PMBOH with Al-MCM-41 gave **2a** in 69% yield. The improved yield may be attributed to the increase in pore size of the catalyst.



This method was extended to a variety of alcohols. Thus, the terpenoidal *primary* alcohol nopol (**1b**) and *secondary* alcohol menthol (**1c**) underwent facile protection with the HY zeolite to give **2b** (57%) and **2c** (58%) while **2b** and **2c** were obtained in 69% and 73% yields respectively by use of Al-MCM-41. In a further study, 1-tetrahydro-pyranyloxy-4-butanol (**1d**), 1-(*tert*-butyldimethylsilyloxy)-4-butanol (**1e**) and 1-benzyloxy-4-butanol (**1f**) gave the expected products **2d** (71%), **2e** (59%) and **2f** (68%) with HY under these reaction conditions, where the acid- and base-sensitive groups remained intact. In the presence of Al-MCM-41, alcohol **1f** gave **2f** in 79% yield; however, **1d** and **1e** with the same catalyst gave **2d** and **2e** in very poor yields.

Furthermore, in the presence of the HY zeolite (pore size = 7.4 Å), the sugar alcohol, 1,2,3,4- di-*O*-isopropylidene-D-galactopyranoside (**1g**), gave product **2g** only in 25% yield after a prolonged period. However, **2g** was obtained in 69% yield in the presence of Al-MCM-41, presumably because of the increase in pore size and surface area (pore size = 30 Å Si/Al = 30; surface area = 991 m^2/g). This conversion, however, required 20 h. The acid sensitive acetonide groups are compatible with the Al-MCM-41 catalyst. With 1,2-*O*-isopropylidene-3-methoxy-D-glucofuranoside (**1h**) and 1,2-*O*-isopropylidene-D-xylo-furanoside (**1i**), the mono-protected products **2h** (75%) and **2i** (72%) were obtained respectively as the exclusive products using Al-MCM-41.

Table 2. PMB Protection of Alcohols over HY and Al-MCM-41.

Cmpd	Yield (%)		Time(h)
	HY	Al-MCM-41	
 2a	56	69	12
 2b	57	69	12
 2c	58	73	12
 2d	71	38	12
 2e	59	32	12
 2f	68	79	12
 2g	25	69	20
 2h	----	75	20
 2i	----	72	20

In order to check their regenerability, both catalysts HY zeolite (0.400 g) and Al-MCM-41 from the reaction of **1a** with *p*-methoxybenzyl alcohol were washed with EtOAc and reactivated by calcination in air at 400°C for 3 h; they were recycled for four runs without significant loss of activity. The X-ray diffraction patterns of the freshly used and regenerated catalysts revealed that they retained their crystallinity throughout.

Table 3. Reusability of the Catalysts for PMB Protection of Octanol (**1a**)

Cycle #	Yield (%)	
	HY	Al-MCM-41
1	56	69
2	54	66
3	54	65.5
4	52	64

Thus, in conclusion these examples illustrate that the use of zeolites is a novel and efficient method for the selective protection of alcohols using inexpensive and regenerable catalyst systems. The merits of the present method are high selectivity for primary alcohols, low cost and simple work-up, reusability and tolerance to a wide variety of acid- and base- sensitive functional groups.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded using Varian FT 200 MHz (Gemini) instrument with TMS as the internal standard and $CDCl_3$ as the solvent. Mass spectra were recorded on VG Micro mass 7070 H.

Typical Procedure.- To a solution of **1h** (0.234 g, 1.0 mmol) in CH_3NO_2 (5 mL), were added *p*-methoxybenzyl alcohol (0.138 g 1.0 mmol), the catalyst (HY/Al-MCM-41 zeolite, 0.100 g) and the mixture was stirred for 12 h at 50°C. The reaction mixture was filtered to remove the catalyst and the catalyst was washed with EtOAc (2 x 10 mL), dried (Na_2SO_4), evaporated under reduced pressure and the residue purified by column chromatography (60-120 mesh SiO_2, 5% EtOAc in hexane) to give 0.27 g (76%) of **2h** as a pale yellow syrup.

Heptyloxymethyl-4-methoxybenzene (2a), colorless syrup. ^{1}H NMR: δ 6.82, 7.21 (2d, 4H, J = 9.04 Hz), 4.39 (s, 2H), 3.78 (s, 3H), 3.39 (t, 2H, J = 7.14 Hz), 1.48-1.63 (m, 2H), 1.20-1.38 (m, 10H), 0.82-0.93 (m, 3H). EIMS: *m/z* (relative intensity in %): 250 (M^+, 7.5), 228 (2.5), 197 (2.0), 121 (100), 57 (8.7).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.71; H, 10.39

2-[2-(4-Methoxybenzyloxy)ethyl]-6,6-dimethyl bicyclo[3.1.1]hept-2-ene (2b), pale yellow syrup. ^{1}H NMR: δ 6.79, 7.18 (2d, 4H, J = 8.57 Hz), 5.18-5.24 (m, 1H), 4.38 (s, 2H), 3.78 (s, 3H), 3.40 (t, 2H, J = 7.14 Hz), 2.13-2.38 (m, 4H), 1.92-2.10 (m, 2H), 1.24 (s, 3H), 0.92-1.18 (m, 2H), 0.79 (s, 3H). EIMS: *m/z* (relative intensity in %): 286 (M^+, 3.7), 228 (26.5), 197 (18.7), 121 (100), 41 (55.0).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.67; H, 9.12

1-Isopropyl-2-(4-methoxybenzyloxy)-4-methyl-(1*S*, 2*R*, 4*R*)-cyclohexane (2c), yellow syrup . ^{1}H NMR: δ 7.25, 6.85 (d, J = 8.5 Hz, 4H), 4.45(s, 2H), 3.80(s, 3H), 3.40 (dt, J = 9.7, 4.2 Hz, 1H) 2.25-2.10 (m,1H), 2.00-1.90(m,1H), 1.70-1.57(m, 2H), 1.10-0.85(m, 11H), 0.80(d, J = 3.4Hz, 3H); EIMS: *m/z* 276(M$^+$). HRMS: Calcd for $C_{18}H_{28}O_2$ 276.208930. Found 276.207990.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.17; H, 10.21

1-(4-Methoxybenzyloxy)-6-tetrahydro-2*H*-2-pyranyloxybutane (2d), light yellow syrup. ^{1}H NMR: δ 7.22, 6.83 (d, J = 8.4 Hz, 4H), 4.55 (brs, 1H), 4.40 (s, 2H), 3.88-3.75 (m, 5H), 3.50-3.30 (m, 4H), 1.90-1.30(m, 10H). EIMS: *m/z* 294(M$^+$).

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.34; H, 8.84

1-(4-Methoxybenzyloxy)-*tert*-butyldimethylsilyloxy-4-butanol (2e), honey color syrup. ^{1}H NMR: δ 7.28, 6.90 (d, J = 8.8 Hz, 4H), 4.44 (s, 2H), 3.88 (s, 3 H), 3.62 (t, J = 6.3 Hz, 2H), 3.42(t, J = 7.1 Hz, 2H), 1.43-1.30 (m, 4H), 0.90 (s, 9H), 0.06 (s, 6H). EIMS: *m/z*: 324 (M$^+$).

Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.57; H, 10.06

1-(4-Benzyloxybutoxymethyl)-4-methoxybenzene (2f), light yellow syrup. ^{1}H NMR: δ 8.02 (d, J = 7.5 Hz, 2H), 7.55-7.35 (m, 3H) 7.20 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 4.40 (s, 2H), 4.10 (t, J = 6.2 Hz, 2H) 3.70 (s, 3H), 3.40 (t, J = 6.2 Hz, 2H), 1.80-1.40 (m, 4H). EIMS: *m/z* 314 (M$^+$).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.56; H, 6.97

5-(4-Methoxybenzyloxy)-2, 2, 7, 7-tetramethylperhydrodi[1,3]dioxolo[4,5-*b*-:5,4]-*d*-pyran (2g), honey color syrup. ^{1}H NMR: δ 7.35, 6.85 (d, J = 8.8 Hz, 2H,) 5.50 (d, J = 5.1 Hz, 1H), 4.58-4.48 (m, 3H), 4.30-4.20 (m, 2H), 3.90 (dt, J = 6.0,2.3 Hz, 1H), 3.80 (s, 3H), 3.63-3.50 (m, 2H), 1.53 (s, 3H), 1.45 (s, 3H), 1.31 (s, 6H). FABMS: *m/z* 379 (M-1). HRMS: Calcd for $C_{20}H_{28}O_7$ 379.17569. Found 379.176152.

Anal. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 63.12; H, 7.42

2-(4-Methoxybenzyloxy)-1-(6-methoxy-2-2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)perhydrofuro- [2,3-*d*][1,3]dioxol-5-yl]-(1R)-ethan-1-ol (2h), pale yellow syrup. ^{1}H NMR: δ 6.80, 7.20 (2d, 4H, J = 8.78 Hz) 5.79 (d, 1H, J = 3.41 Hz), 4.42-4.52 (m, 3H), 3.96-4.03 (m, 2H), 3.70-3.78 (m, 4H), 3.48-3.70 (m, 2H), 3.40 (s, 3H), 2.50-2.62 (brs, 1H),1.27, 1.42 (2s, 6H). EIMS: *m/z* (relative intensity in %): 354 (M$^+$, 3.7), 209 (8.7), 173 (10.0), 121 (100), 87 (65.0).

Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.00; H, 7.39. Found: C, 60.98; H, 6.91

6-Methoxy-5-[2-(4-methoxybenzyloxy)ethyl]-2,2-dimethyl-(3a*R*, 5*R*, 6*S*, 6a*R*)-perhydro furo[2,3-*d*-][1,3]dioxole (2i), yellow syrup. ^{1}H NMR: δ 7.24, 6.86 (2d, 4H, *J* = 5.71 Hz), 5.92 (d, 1H, *J* = 2.85 Hz), 4.42-4.60 (m, 3H), 4.18-4.20 (m, 2H), 3.73-3.90 (m, 5H), 3.50-3.60 (br. s, 1H), 1.30, 1.44 (2s, 6H). EIMS: *m/z* (relative intensity in %) 310 (M$^+$, 3.7), 179 (4.0), 137 (25.2), 121 (100), 78 (25.0).

Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.91; H, 6.91

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