J. Org. Chem. **1999,** *64,* 8943−8944 **8943**

A Facile Conversion of Alcohols into *p*-Methoxybenzyl Ethers (PMB-ethers) Using *p*-Methoxybenzyl Alcohol−Yb(OTf)$_3$[†]

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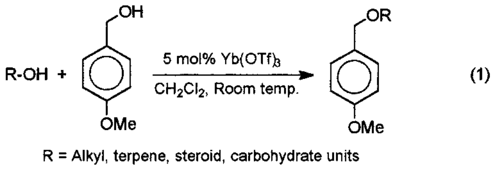
Received March 30, 1999

The correct choice of an efficient protecting group[1] is often decisive for the completion of the successful synthesis of a complex molecule, for which the strategy should take into account the different requirements that are present in the molecule. Protection of a hydroxyl functionality as the benzyl ether is preferred as a permanent protective group. However, the choice of oxidation-labile benzyl groups, such as *p*-methoxybenzyl (PMB) and 3,4-dimethoxybenzyl (DMB), proved its worth as a result of the ease with which these groups undergo deprotection under almost neutral conditions[2] (DDQ, aqueous dichloromethane). Conventionally, the PMB protection is achieved under strongly basic conditions[3,4] (PMB−halides, NaH, or NaOH), in which alkali-labile protective groups are lost. Alternatively, PMB−trichloro acetimidate[5] has been developed, in which the substrate is exposed to acids for a longer duration, and PMB−diazomethane[6] is not a desirable reagent of choice. Hence, a better protocol is warranted for PMB protection, which would preserve the integrity of both alkali- and acid-labile protective groups. The unique potential of the PMB group in organic synthesis, particularly in carbohydrate chemistry, prompted us to describe mild and potential reaction conditions for PMB protection, using PMB alcohol−Yb(OTf)$_3$ (eq 1).



(1)

Rare earth (III) salts such as triflates[7] are advantageously utilized as versatile Lewis acids in several organic reactions. Our recent work[8] on deprenylation using Yb(OTf)$_3$ through prenyl carbocation indicated it to be the right catalyst for effecting the PMB protection of alcohols with PMB alcohol, whose oxidation potential ($E_{1/2}$ 1.22 V) would facilitate the generation of carbocation.

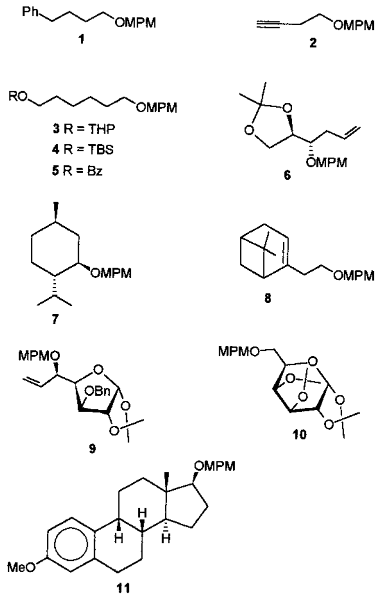


Figure 1. Representative PMB ethers. All of the compounds were characterized by ^{1}H NMR. All of the reactions were carried out using 5 mol % catalyst at room temperature, and isolated yields are reported.

Table 1

entry	compd	time (h)	yield (%)	entry	compd	time (h)	yield (%)
1	**1**	4	80	6	**6**	32	60
2	**2**	8	87	7	**7**	30	80
	2[a]	3	84	8	**8**	24	83
3	**3**	32	75	9	**9**	24	82
4	**4**	36	71	10	**10**	28	85
5	**5**	36	76	11	**11**	30	88

[a] 10 mol % of yb(OTf)$_3$ used.

Initially, the reaction of 4-phenyl butanol with PMB alcohol (2 equiv) in the presence of Yb(OTf)$_3$ (5 mol %) was carried out in different solvents such as CH_3CN, CH_3NO_2, and CH_2Cl_2 independently to give the product in 42%, 59%, and 80% yield, respectively. The byproduct, diPMB ether formed by dehydration, also was found to react with alcohol to give the product, leaving behind 10−15% of the dimer.

Having established the preferred reaction conditions, PMB protection of several representative alcohols[9] (Figure 1) was performed to demonstrate the versatility and uniqueness of the present reaction conditions (Table 1). Entry 2 depicts an acetylenic alcohol wherein rate enhancement of the reaction was observed with 10 mol % of catalyst, and entries 3 and 4 show the tolerance of reaction conditions to both the THP and TBS ethers. Entry 5 is a representative example for a benzoate ester, in which the Bz group survives the reaction conditions, and entry 6 depicts an example where the 1°,2° acetonide

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[†] IICT communication 4272.

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[9] The starting materials for the preparation of compounds **1**, **2**, **7**, **8**, **10**, and **11** are commercial samples. Compounds **6** and **9** were prepared from the corresponding known aldehydes by Grignard reaction with the respective bromides. Compounds **3**−**5** were prepared by known methods from the commercially available diol.

10.1021/jo990563x CCC: $18.00

is intact. Entries 7 and 8 represent the terpenes, and entries 9 and 10 represent carbohydrates in which allylic as well as 1° alcohols were successfully protected without effecting acetonides. Entry 11 represents an example of a steroid. However, in the present reaction conditions, tertiary alcohols were found to be unreacted. The results of the present study, indicated in Table 1, amply demonstrate the efficiency of PMB alcohol−Yb(OTf)$_3$ in effecting PMB protection under mild conditions on a wide spectrum of compounds.

Thus, the merits of the present protocol are (a) compatibility to both the acid- and alkali-labile protecting groups, (b) use of PMB alcohol rather the derivatives (PMB−halide, PMB−trichloroacetimidate, PMB−diazomethane) for the first time, (c) use of Yb(OTf)$_3$ as catalyst (5 mol %), making this an environmentally friendly protocol, and (d) tolerance of a wide variety of functional groups and substrates. The present protocol for PMB protection of hydroxy groups thus would find a wide acceptability in organic synthesis, particularly in carbohydrate chemistry.

Experimental Section

Typical Procedure for PMB Protection with Yb(OTf)$_3$. A solution of 4-phenylbutanol (150 mg, 1.0 mmol) and *p*-methoxybenzyl alcohol (276 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was treated with Yb(OTf)$_3$ (31 mg, 0.05 mmol) and stirred at room temperature. At the completion of the reaction (TLC analysis), the reaction mixture was diluted with water (10 mL), and the two layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 × 5 mL), and the combined organic layers were washed with water (2 × 5 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Purification of the crude residue by column chromatography (silica gel, 1:9 ethyl acetate−hexane) gave 1-*p*-methoxybenzyl 4-phenylbutanol (**1**) (216 mg) in 80% yield along with di-*p*-methoxybenzyl ether (12%).

Spectral Data for Selected Compounds. ^{1}H NMR (200 MHz, $CDCl_3$, TMS, δ in ppm): **data for 3**, 1.30−1.90 (m, 14H), 3.30−3.50 (m, 4H), 3.75−3.88 (m, 5H), 4.40 (s, 2H), 4.55 (bs, 1H), 6.83 (d, 2H, J = 4.34 Hz), 7.22 (d, 2H, J = 4.34 Hz), MS (EI) 237 ($M^+ - 85$), HRMS calcd for $C_{14}H_{21}O_3$ 237.149070, obsd 237.149152; **data for 4**, 0.9 (s, 9H), 1.30−1.43 (m, 4H), 1.48−1.67 (m, 4H), 3.45 (t, 2H, J = 3.52 Hz), 3.62 (t, 2H, J = 3.52 Hz), 3.83 (s, 3H), 4.44 (s, 2H), 6.90 (d, 2H, J = 4.70 Hz), 7.28 (d, 2H, J = 4.70), MS (EI) 295 ($M^+ - 57$), HRMS calcd for $C_{15}H_{27}O_3$-Si 295.172948, obsd 295.171520; **data for 5**, 1.40−1.80 (m, 8H), 3.40 (t, 2H, J = 2.47 Hz), 3.80 (s, 3H), 4.30 (t, 2H, J = 2.47 Hz), 4.40 (s, 2H), 6.80 (d, 2H, J = 3.45 Hz), 7.20 (d, 2H, J = 3.45 Hz), 7.35−7.55 (m, 3H), 8.02 (d, 2H, J = 2.96 Hz), MS (EI) 342 (M^+), HRMS calcd for $C_{21}H_{26}O_4$ 342.183110, obsd 342.181705; **data for 7**, 0.80 (d, 3H, J = 3.48 Hz), 0.85−1.10 (m, 11 H), 1.57−1.70 (m, 2H), 1.90−2.00 (m, 1H), 2.10−2.25 (m, 1H), 3.40 (dt, 1H, J = 5.18, 2.07), 3.80 (s, 3H), 4.45 (s, 2H), 6.85 (d, 2H, J = 4.41 Hz), 7.25 (d, 2H, J = 4.41 Hz), MS (EI) 276 (M^+), HRMS calcd for $C_{18}H_{28}O_2$ 276.208930, obsd 276.207990; **data for 9**, 1.28 (s, 3H), 1.47 (s, 3H), 3.85 (m, 4H), 4.15 (m, 2H), 4.35−4.65 (m, 5H), 5.28−5.38 (m, 2H), 5.63−5.80 (m, 1H), 5.95 (d, 1H, J = 1.91 Hz), 6.80 (d, 2H, J = 4.03 Hz), 7.30−7.42 (m, 7H), FABMS 449 ($M^+ + Na$); **data for 10**, 1.31 (s, 6H), 1.45 (s, 3H), 1.53 (s, 3H), 3.50−3.63 (m, 2H), 3.80 (s, 3H), 3.90 (dt, 1H, J = 2.40, 1.00 Hz), 4.20−4.30 (m, 2H), 4.48−4.58 (m, 3H), 5.50 (d, 1H, J = 1.92 Hz), 6.85 (d, 2H, J = 3.46 Hz), 7.35 (d, 2H, J = 3.46 Hz), FABMS 379 ($M^+ - 1$), HRMS calcd for $C_{20}H_{27}O_7$ 379.175679, obsd 379.176152; **data for 11**, 0.80 (s, 3H), 1.10−1.67 (m, 8H), 1.73−2.30 (m, 5H), 2.80 (m, 2H), 3.40 (m, 1H), 3.70 (s, 3H), 3.75 (s, 3H), 4.42 (s, 1H), 6.50 (s, 1H), 6.60 (d, 1H, J = 4.39 Hz), 6.75 (d, 2H, J = 4.40 Hz), 7.10 (d, 1H, J = 3.96 Hz), 7.15 (d, 2H, J = 4.40 Hz), MS (EI) 406 (M^+), HRMS calcd for $C_{27}H_{34}O_3$ 406.250795, obsd 406.248844.

Acknowledgment. One of the authors, A. K. Mahalingam, is thankful to CSIR, New Delhi for financial support.

JO990563X