An Efficient Method for the *p*-Methoxybenzylation of Hydroxy Groups with 2-(4-Methoxybenzyloxy)-3-nitropyridine

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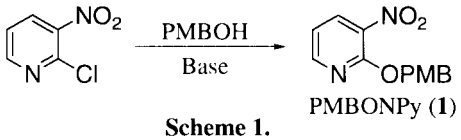
2-(4-Methoxybenzyloxy)-3-nitropyridine (PMBONPy), easily prepared from 2-chloro-3-nitropyridine and *p*-methoxybenzyl (PMB) alcohol, reacts with various types of hydroxy groups in the presence of a catalytic amount of trimethylsilyl triflate (Me_3SiOTf) to give the corresponding PMB ethers in high yields under mild conditions.

In multistep syntheses of complex molecules such as natural products, it is often important to differenciate a certain hydroxy group from other hydroxy groups within the same molecule. For that purpose, selective protection by using different types of protecting groups at each synthetic stage has been tried. For example, esters, acetals or silyl ethers which are generally deprotected under alkaline or acid conditions are used as the protecting groups. Because of their inertness under the above conditions, benzyl ethers, on the other hand, are employed as long-lasting protecting groups and are mildly removed at the latter stages of multistep syntheses. Of those frequently employed benzyl ethers, PMB ether[1] is one of the most useful benzyl-type protecting groups since it is selectively deprotected by DDQ-oxidation. If properly chosen, therefore, benzyl-type protecting groups such as PMB, benzyl or halobenzyl[2] increase synthetic possibilities. However, benzyl protection of alcohols is often accompanied by serious side reactions especially in the case of complex molecules bearing alkali-sensitive functional groups since it is usually carried out under strongly alkaline conditions such as combinations of benzyl halides and alkali metal alkoxides. It was reported that PMB ethers were prepared also by the use of PMB trichloroacetimidate[3,4] under mildly acidic conditions, which were compatible with alkali- and acid-sensitive protecting groups within the same molecule. However, PMB trichloroacetimidate was not stable enough to give PMB ethers constantly in high yields.[4] We would like to report here about 2-(4-methoxybenzyloxy)-3-nitropyridine, a stable and practically-useful *p*-methoxybenzylating reagent for hydroxy groups, which gave PMB ethers in high yields under mild conditions.

Recently, a practical method for benzylation of alcohols with benzyl mesylate by using a catalytic amount of lithium tetrakis(pentafluorophenyl)borate in the co-existence of lithium triflate and magnesium oxide was reported from our laboratory.[5] However, *p*-methoxybenzylation of alcohols did not proceed by the above method because of the instability of the PMB mesylate. On the other hand, it was previously established that 2-alkoxy-3,5-dinitropyridines reacted with thiols in the presence of Lewis acids to give the corresponding sulfides in good yields.[6] Later, Kusumoto et al. reported that 3-nitro-2-pyridyl glycoside, a glycosyl donor, could be used in glycosylation reactions in the presence of a catalytic amount of a Lewis acid.[7] These results suggested that 2-alkoxynitropyridines were activated by Lewis acids and worked as alkylating agents. 2-(4-Methoxybenzyloxy)-3-nitropyridine (PMBONPy, **1**), a new *p*-methoxybenzylating reagent, was then prepared from PMB alcohol and 2-chloro-3-nitropyridine in 78% yield according to the procedure reported by Ballesteros[8] (Scheme 1): i.e., to a suspension of PMB alcohol (45 mmol), powdered potassium hydroxide (120 mmol), and potassium carbonate (30 mmol) in dry toluene (200 mL) were successively added 2-chloro-3-nitropyridine (30 mmol) and tris(3,6-dioxaheptyl)amine (3 mmol). After the reaction mixture was stirred for 1 h at room temperature, it was worked up by usual procedure. The residue was purified by recrystallization (hexane–isopropyl ether) to give **1** (6.1 g, 78%, mp 75–77 °C) as a pale yellow powder which can be stored at room temperature for a month long. Thus formed **1** was easy to be handled because it was powdery and was moisture-resistant.



Scheme 1.

In the first place, *p*-methoxybenzylation of 2-phenylethanol (**2**) with 1.5 equiv of **1** was tried by using 0.5 mol% of Me_3SiOTf in dichloromethane, and within the next 5 min the desired product **3** was obtained in 90% yield as expected (Table 1, entry 1).[9] When other solvents such as toluene, benzotrifluoride (BTF) and diethyl ether were used under the above conditions, the reactions likewise proceeded smoothly and gave **3** in good yields (entries 2–4). When only 0.3 mol% of trityl tetrakis(pentafluorophenyl)borate ($TrB(C_6F_5)_4$) or triflic acid (TfOH) was used, the *p*-methoxybenzylation was completed smoothly, especially with the former catalyst which proceeded in less than 5 min (entries 5 and 6).[10] When **2** was treated with **1** in

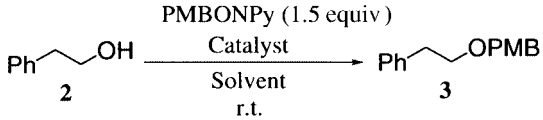


Table 1. Effect of catalysts and solvents on *p*-methoxybenzylation of 2-Phenylethanol

Entry	Catalyst (mol%)	Solvent	Time	Yield/%
1	Me_3SiOTf (0.5)	CH_2Cl_2	5 min	90
2	Me_3SiOTf (0.5)	Toluene	5 min	86
3	Me_3SiOTf (0.5)	BTF	5 min	81
4	Me_3SiOTf (0.5)	Et_2O	5 min	89
5	$TrB(C_6F_5)_4$ (0.3)	BTF	5 min	90
6	TfOH (0.3)	BTF	20 min	82
7	MsOH (5.0)	CH_2Cl_2	15 h	93
8	CSA (5.0)	CH_2Cl_2	15 h	91

the presence of 5 mol% of methanesulfonic acid (MsOH) or 10-camphorsulfonic acid (CSA) in dichloromethane, **3** was obtained in high yield though the reaction proceeded slowly (entries 7 and 8). On the other hand, the conventional *p*-methoxybenzylation of **1** with PMB trichloroacetimidate gave **3** in 77% yield.[4]

Encouraged by the above results, the *p*-methoxybenzylation of several alcohols with **1** was tried (Table 2). When alcohols bearing alkali-sensitive ester groups were treated with **1** in the presense of Me_3SiOTf (1.0–1.1 mol%) in dichloromethane, the reactions proceeded smoothly and gave the corresponding PMB ethers in high yields (entries 1–5). It is noted that secondary and tertiary alcohols were *p*-methoxybenzylated without any difficulties, which clearly indicated the merit of the present method superior to the conventional ones. Furthermore, neither epimerization at the α-position of ester carbonyl groups (entries 1, 3 and 5) nor elimination of β-hydroxy carbonyl compounds (entries 1, 2, 5 and 8) was observed during the *p*-methoxybenzylation. Other alkali-sensitive groups such as acryloyloxy, halo or keto groups were unaffected (entries 6–10), and alcohols bearing even acid-sensitive protecting groups such as acetals or silyloxy group gave the protected products in high yields (entries 11 and 12) under the present conditions.

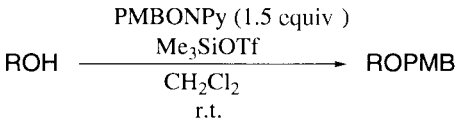
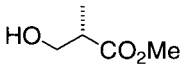
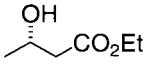
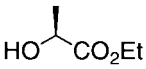
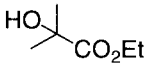
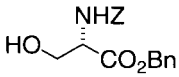
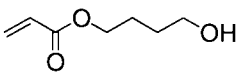
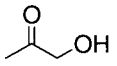
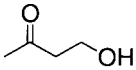
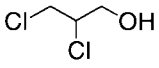
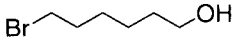
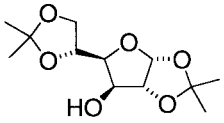
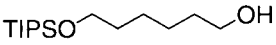


Table 2. *p*-Methoxybenzylation of alcohols with PMBONPy by using a catalytic amount of Me_3SiOTf

Entry	Alcohol	Me_3SiOTf /mol%	Time /min	Yield /%
1		1.1	10	91
2		1.0	10	89
3		1.0	30	quant.
4		1.0	30	74
5		1.1	5	90
6		0.7	5	87
7		0.9	5	83[a]
8		0.5	5	93
9		0.9	5	90
10		1.2	5	85
11		1.4	5	87[a]
12		0.8	5	85

[a]PMBONPy (2.0 equiv) was used.

General procedure for the preparation of PMB ethers is as follows: to a stirred solution of alcohol (0.5 mmol) and PMBONPy (0.75 mmol) in dichloromethane (1.5 mL) under argon atmosphere was added a solution of Me_3SiOTf (0.5–1.4 mol%) in dichloromethane (0.1 mL) at 0 °C. The reaction was allowed to warm up to room temperature and stirred for 5–30 min. After the completion of reaction (detected by TLC), it was quenched with saturated aqueous sodium hydrogencarbonate solution and the mixture was extracted with dichloromethane. Organic layers were dried with anhydrous magnesium sulfate and evaporated, and the residue was purified by preparative TLC or silica-gel column chromatography to afford the corresponding PMB ethers in high yields.

It is noted that a new reagent **1** which is moisture- and air-resistant and easy to be handled is quite useful in the *p*-methoxybenzylation of various hydroxy groups even in the cases of alcohols bearing alkali- or acid-sensitive functional groups.

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References and Notes

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