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Graphical Abstract

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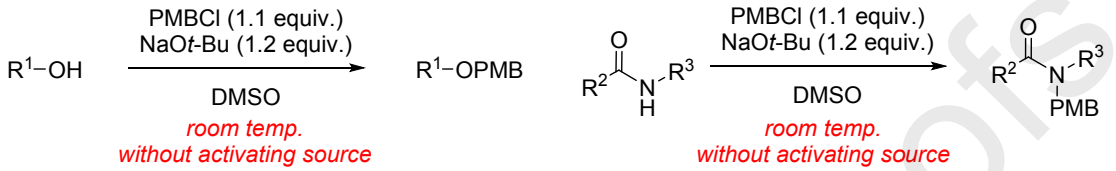

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Simple and Rapid *p*-Methoxybenzylation of Hydroxy and Amide Groups at Room Temperature by NaO*t*-Bu and DMSO

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ABSTRACT

The *p*-methoxybenzylation of hydroxy and amide groups by *p*-methoxybenzyl chloride utilizing NaO*t*-Bu in DMSO is described. *p*-Methoxybenzylation of sterically hindered menthol using NaO*t*-Bu in DMSO proceeded faster than the commonly used methods which use NaH in THF or DMF for *p*-methoxybenzylation of hydroxy and amide groups. The described method was applicable for sterically hindered substrates at room temperature without adding any activating reagents such as tetrabutylammonium iodide.

1. Introduction

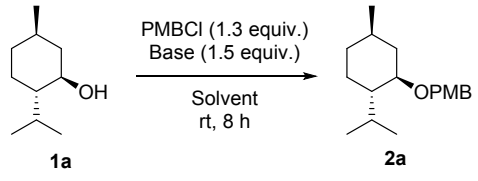
Benzyl and benzyl-derived protecting groups are widely used to protect alcohols and amine derivatives.[1] The *p*-methoxybenzyl (PMB) group, in particular, is widely employed as it is generally stable under a variety of reaction conditions and can be selectively deprotected by oxidizing reagents such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or ceric ammonium nitrate (CAN).[1,2] Due to the usefulness of the PMB group as a protecting group, its protection methods have been well developed. Nucleophilic substitutions of alcohols or amine derivatives with *p*-methoxybenzyl chloride (PMBCl)[3] have been most commonly used. Acid-catalyzed coupling reactions with PMB 2,2,2-trichloroacetimidate[4] have also often been employed for *p*-methoxybenzylation of alcohols. Moreover, a number of alternative methods using imidate-type reagents,[5] anisyl alcohols,[6] and other methods[7] have been developed for the protection of alcohols.

Despite the large number of methods which have been developed for *p*-methoxybenzylation, nucleophilic reactions between alcohols or amine derivatives and PMBCl have been most commonly used due to their simplicity, reliability, and cost-effectiveness. [3] The strong base NaH in either THF or DMF has been the most commonly used condition for this reaction. However, these methods often require high temperatures and an activator such as tetrabutylammonium iodide (TBAI).[1] Furthermore, NaH is an undesired base for large scale processes, as it is insoluble in most solvents and generates highly explosive hydrogen gas.[8] Recently, tertiary amine-mediated simple and mild *p*-methoxybenzylation has been reported.[9] Although this method is applicable under weak basic conditions, it also requires high temperatures and sodium iodide as an additive to achieve *p*-methoxybenzylation of sterically hindered alcohols. Herein, we describe simple and rapid *p*-methoxybenzylation of hydroxy and amide groups by PMBCl at room temperature using NaO*t*-Bu in DMSO. [10]

2. Results

In order to develop the highly reactive *p*-methoxybenzylation method at room temperature, we investigated the suitable reaction conditions for sterically hindered menthol **1a** (Table 1). Treatment of **1a** and PMBCl with NaH in THF and DMF, respectively, produced **2a** in 1% and 53% yields, respectively (entries 1 and 2). The addition of 10 mol% of TBAI did not enhance the chemical yield (entry 3). To enhance the reactivity of this nucleophilic substitution and increase the chemical yield, we employed DMSO, which is a solvent with greater polarity than DMF (entry 4). As expected, this reaction condition enhanced the yield slightly (68%) compared to NaH/DMF. After examining NaO*t*-Bu and KO*t*-Bu as bases (entries 5 and 6), NaO*t*-Bu was found to be the most suitable for this reaction. Treatment of **1a** with 1.3 equivalents of PMBCl and 1.5 equivalents of NaO*t*-Bu in DMSO at room temperature afforded PMB ether **2a** in a 95% yield (entry 5). Replacing DMSO with DMF decreased the yield of **2a** (entry 7). In addition to these positive results, NaO*t*-Bu is a base which is suitable for large scale processes due to its safety and cost-effectiveness.[8a] For these reasons, we feel that the NaO*t*-Bu/DMSO system is a superior method for *p*-methoxybenzylation of sterically hindered hydroxy groups.

Table 1. *p*-Methoxybenzylation of **1a** with PMBCl



Entry	Base	Solvent	Yield (%)[a]
1	NaH	THF	1
2	NaH	DMF	53
3[b]	NaH	DMF	47
4	NaH	DMSO	68
5	NaO*t*-Bu	DMSO	95
6	KO*t*-Bu	DMSO	93
7	NaO*t*-Bu	DMF	79

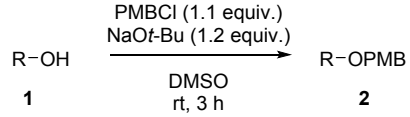
[a] Yields were determined by ^{1}H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

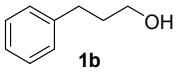
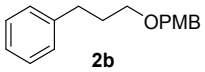
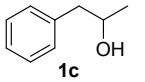
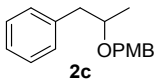
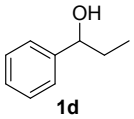
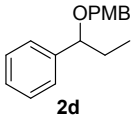
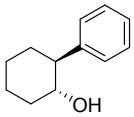
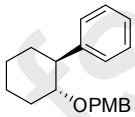
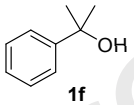
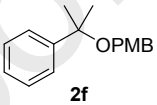
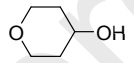
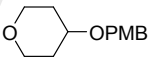
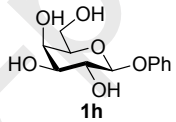
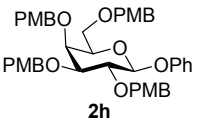
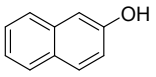
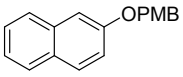
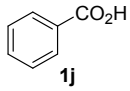
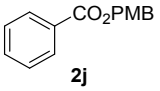
[b] 10 mol% of TBAI was added as an additive.

To investigate the scope of the *p*-methoxybenzylation, we treated various alcohols with PMBCl and NaO*t*-Bu in DMSO at room temperature (Table 2).

Treatment of the primary alcohol **1b** with 1.1 equivalents of PMBCl and 1.2 equivalents of NaO*t*-Bu in DMSO at room temperature for 3 h gave PMB ether **2b** in a nearly quantitative yield (entry 1). The reaction of secondary alcohols **1c**–**d** afforded the corresponding PMB ethers (**2c**–**d**), respectively, in excellent yields (99 and 93%; entries 2 and 3, respectively). Sterically hindered alcohols such as **1e** and **1f**[11] were also converted into **2e** and **2f**, respectively, in good yields (98 and 84%; entries 4 and 6, respectively). On the other hand, treatment of **1e** and **1f** with PMBCl and NaH, respectively, in DMF diminished the yields (40 and 41%; entries 5 and 7, respectively). Secondary alcohols containing a tetrahydropyran ring (**1g**) were also converted into PMB ether at a 93% yield (entry 8). Galactopyranoside **1h** was treated with 4.8 equivalents of PMBCl and NaO*t*-Bu to produce the tetrabenzylated product **2h** in good yield (entry 9). This reaction was also applicable to 2-naphthol (**1i**) whose conjugate base is less nucleophilic than that of the alcohols (entry 10). On the other hand, benzoic acid **1j** converted into PMB ester **2j** in a lower yield than the alcohols and naphthol (entry 11). In addition to *p*-methoxybenzylation, NaO*t*-Bu/DMSO system was effective for benzylation as well as 2,3- and 2,4-dimethoxybenzylation (See the supporting information).

Table 2. Substrate scope of *p*-methoxybenzylation of hydroxy groups



Entry	Substrate	Product	Yield (%)[a]
1	 **1b**	 **2b**	99
2	 **1c**	 **2c**	99
3	 **1d**	 **2d**	93
4	 **1e**	 **2e**	98
5[b]			40
6[c]	 **1f**	 **2f**	84
7[d]			41
8	 **1g**	 **2g**	93
9[e]	 **1h**	 **2h**	88
10[e]	 **1i**	 **2i**	96
11[f]	 **1j**	 **2j**	44

[a] Isolated yield.

[b] Reaction was run using 1.2 equiv. of NaH and DMF instead of NaO*t*-Bu and DMSO.

[c] Reaction was run using 1.5 equiv. of NaO*t*-Bu and PMBCl.

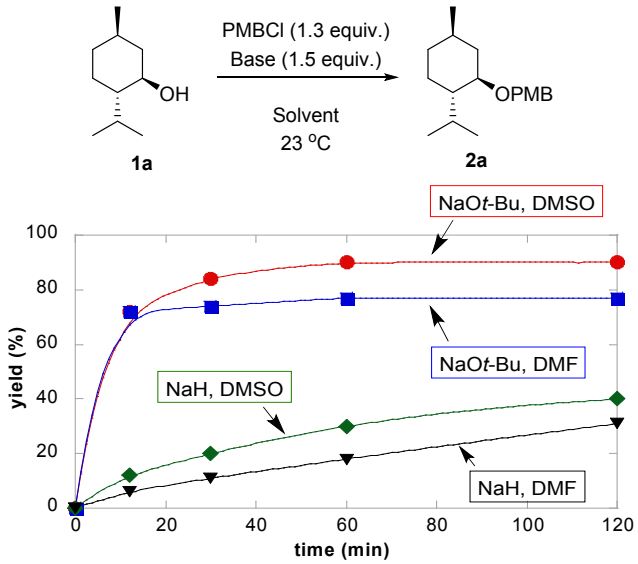
[d] Reaction was run using 1.5 equiv. of NaH and DMF instead of NaO*t*-Bu and DMSO.

[e] Reaction was run using 4.8 equiv. of NaO*t*-Bu and PMBCl.

[f] Reaction was run for 5 h.

As shown by the investigations detailed in Tables 1 and 2, the NaO*t*-Bu/DMSO system gave high yields in the *p*-methoxybenzylation of sterically hindered alcohols compared with the NaH/THF and NaH/DMF systems. This difference in outcomes seems to be due to a difference in reaction rates. Therefore, we conducted a close comparison of the reactivities of the NaH/DMF, NaH/DMSO, NaO*t*-Bu/DMF, and NaO*t*-Bu/DMSO systems using alcohol **1a** as a substrate (Scheme 1). It was found that the NaO*t*-Bu/DMSO and NaO*t*-Bu/DMF system afforded PMB ether in a 72% yield 25 min after the reaction started while the NaH/DMSO and NaH/DMF systems afforded 12% and 6% yields, respectively, in the same amount of time. These data suggest that NaO*t*-Bu showed higher reactivity than NaH in the *p*-methoxybenzylation of sterically hindered alcohols. The reason why NaO*t*-Bu is more reactive than NaH against **1a** should be due to the higher deprotonation activity of NaO*t*-Bu in

DM
been reported that NaH was not effective for deprotonation of sterically hindered tertiary alcohols.[13]

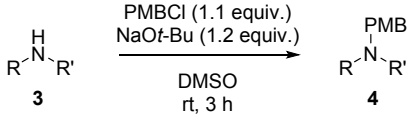


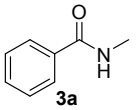
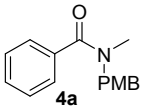
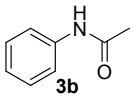
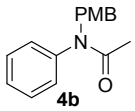
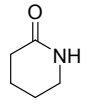
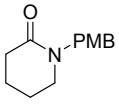
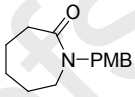
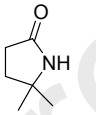
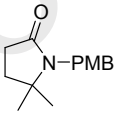
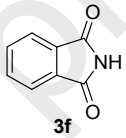
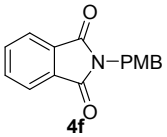
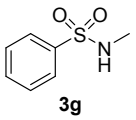
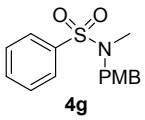
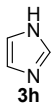
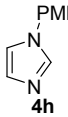
Scheme 1. Comparison of the reactivity between NaO*t*-Bu and NaH.

Next, we investigated *p*-methoxybenzylation of amide, imide, sulfoneamide, and azole compounds using the NaO*t*-Bu/DMSO system at room temperature (Table 3).

N-Methylbenzamide (**3a**) treated with PMBCl and NaO*t*-Bu in DMSO afforded *N*-PMB-*N*-methylbenzenamide (**4a**) in a 99% yield (entry 1). Acetanilide (**3b**) bearing a *N*-phenylamide moiety also provided the desired compound (**4b**) in a 98% yield (entry 2). Cyclic amides such as δ-valerolactam (**3c**) and ε-caprolactam (**3d**) gave **4c** and **4d** in high yields of 78 and 96%, respectively (entries 3 and 4). γ-Lactam (**3e**), possessing a tetra-substituted carbon next to the N-H group, also afforded *N*-p-methoxybenzylation product **4e** selectively in a 93% yield in a short time (entry 5). Imide (**3f**) and sulfonamide (**3g**) were also efficiently converted into the desired products **4f** and **4g**, respectively, in high yields of 92% and 84% (entries 6 and 7). The heteroaromatic compound, imidazole (**3h**), provided the *p*-methoxybenzylated product **4h** in a 97% yield (entry 8). *N*-benzylation of the amide **3a** also proceeded smoothly (See the supporting information).

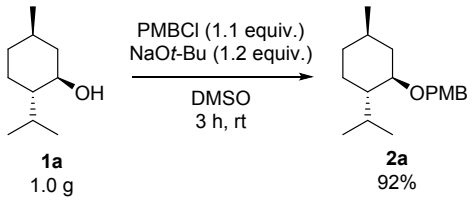
Table 3. *N*-*p*-Methoxybenzylation using NaO*t*-Bu/DMSO system



Entry	Substrate	Product	Yield (%)[a]
1	 **3a**	 **4a**	99
2	 **3b**	 **4b**	98
3	 **3c**	 **4c**	78
4	 **3d**	 **4d**	96
5	 **3e**	 **4e**	93
6	 **3f**	 **4f**	92
7	 **3g**	 **4g**	84
8	 **3h**	 **4h**	97

[a] Isolated yield.

A gram-scale *p*-methoxybenzylation by the NaO*t*-Bu/DMSO system was then examined (Scheme 2). Treatment of 1.0 g of **1a** with 1.1 equivalents of PMBCl and 1.2 equivalents of NaO*t*-Bu resulted in the smooth formation of PMB ether **2a** without obvious loss of reaction efficiency.



Scheme 2. A gram scale synthesis of **2a**

In conclusion, we developed a simple and highly active *p*-methoxybenzylation method for hydroxy and amide groups using PMBCl. NaO*t*-Bu/DMSO showed higher reactivity than the commonly used NaH/THF or DMF, therefore, NaO*t*-Bu/DMSO is an option for use with sterically hindered substrates at room temperature without the need for activating reagents such as an iodide source. This method would be suitable for large-scale synthesis, as it does not require complex reaction conditions or expensive reagents. We have great hopes that the NaO*t*-

Bu... amides will be applicable and useful in fine organic synthesis.

Acknowledgements

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10. To the best of our knowledge, there has been no report of *p*-methoxybenzylation by PMBCl and NaO*t*-Bu in DMSO. Mullens and his coworkers reported *p*-methoxybenzylation of a 2-aminopyrimidine derivative by using PMBCl and NaO*t*-Bu in DMF. See: Mullens, P.; Cleator, E.; McLaughlin, M.; Bishop, B.; Edwards, J.; Goodyear, A.; Andreani, T.; Jin, Y.; Kong, J.; Li, H.; Williams, M.; Zacuto, M.; *Org. Process. Res. Dev.* **2016**, *20*, 1075–1087.
11. *p*-Methoxybenzylation of tertiary alocohol **1f** required 1.5 equiv. of NaO*t*-Bu because *p*-methoxybenzylation of NaO*t*-Bu also proceeded.
12. We investigated deprotonation of **1a** (1.0 equiv.) by NaH (0.5 equiv.) in DMF. The mixture of **1a** and NaH in DMF was stirred at room temperature for 30 min. After the reaction mixture was quenched with aqueous NH_4Cl, gas was generated immediately. This result indicates that H_2 gas was generated after quenching the reaction and, therefore, deprotonation of **1a** by NaH did not proceed smoothly.
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Supplementary Material

Supplementary material related to this article can be found online.

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• *p*-Methoxybenzylation of hydroxy and amide groups using NaO*t*-Bu in DMSO is described.

• Simple, rapid, and cost-effective method.

• *p*-Methoxybenzylation of sterically hindered substrates proceeded at room temperature.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: