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2-Naphthylmethoxymethyl as a Mildly Introducible and Oxidatively Removable Benzyloxymethyl-Type Protecting Group

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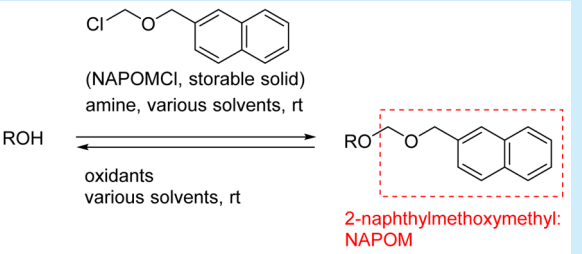
Supporting Information

ABSTRACT: 2-Naphthylmethoxymethyl (NAPOM) was developed for the protection of various hydroxy (including phenolic hydroxy and carboxy) and mercapto groups. The NAPOM group can be introduced in extremely mild conditions (naphthylmethoxymethyl chloride, 2,6-lutidine, room temperature) without concomitant acyl migration in a 1,2-diol system. Furthermore, selective removal of NAPOM in the presence of naphthylmethyl (NAP) and *p*-methoxybenzyl (PMB) groups and, conversely, that of PMB in the presence of NAPOM were realized. These results, as well as its easy handling and compatibility with various solvents, show that NAPOM is a novel and useful choice as a protecting group.



Protecting groups are still playing important roles in the synthesis of complex molecules, despite the recent negative campaign against using them stating that they increase the E-factor and the number of steps. Even in current studies of multistep synthesis, the selection of appropriate protecting groups is sometimes critical. The Benzyl (Bn) group and its substituted analogs form one of the main families of protective groups in synthetic organic chemistry.[1] They have been widely used because of their clean and mild cleavage in reductive conditions (e.g., H_2, Pd/C). Among these, the *p*-methoxybenzyl (PMB) and 2-naphthylmethyl (NAP) groups have been developed, which enable the selective cleavage in the presence of Bn groups by oxidative removal (e.g., with DDQ or CAN).[1]

In contrast to the mildness of deprotection, the introduction of Bn groups suffers from the harsh basic (e.g., NaH, BnBr, DMF; diisopropylethyl amine (DIPEA), BnBr, neat, 150 °C)[2] or acidic (e.g., $BnOC(NH)CCl_3$, TfOH)[3] conditions it requires[4] as well as from the procedure's moisture sensitivity that prevents operation at a small scale or by beginners and nonspecialists. When a substrate is acid or base sensitive, another choice is the benzyloxymethyl (BOM) family, since it allows using a weaker base such as DIPEA for the introduction.[1] Hence, in multistep syntheses, sensitive alcohols requiring oxidative deprotection at a later stage have been protected as *p*-methoxybenzyloxymethyl (PMBOM) ethers.[1]

However, PMBOMCl, which is the most commonly used reagent for introducing the PMBOM group, is known to be labile (storable for less than 3 days at −20 °C),[5] requiring its fresh preparation. In addition, preparation of PMBOMCl also requires a reaction at low temperature (generally −78 °C) that releases sulfur-containing byproducts, which can act as a catalytic poison to transition metals used for hydrogenolysis.[6] Furthermore, even DIPEA sometimes causes side reactions such as acyl migration in 1,2-diol systems.

To solve the problems above, we here report the development of the 2-naphthylmethoxymethyl (NAPOM) group as a new member of the BOM family, which can be introduced under mild conditions and removed under oxidative conditions. It is also easy-to-handle without requiring special attention to moisture and air.

First, as mentioned in the literature,[7] 2-naphthylmethoxymethyl chloride (NAPOMCl) was successfully prepared from 2-naphthylmethyl alcohol and paraformaldehyde catalyzed by gaseous HCl and could be stored in the presence of $CaCl_2$ (neutral drying agent) for more than a year at −20 °C without decomposition.[8] We then examined protection and deprotection of various alcohols as shown in Table 1. Introduction of the NAPOM group was successfully achieved by treatment of primary (**1a**), secondary (**2a**), and tertiary (**3a**) alcohols, a carboxylic acid **4a**, a phenol **5a**, and even a thiol **6a** with NAPOMCl in the presence of DIPEA and $CaCl_2$[9] in CH_2Cl_2 at rt (entries 1−6). Although the use of excess reagent (3 equiv of NAPOMCl and 6 equiv of DIPEA) and a prolonged reaction time (32.5 h) were required for the protection of the tertiary alcohol **3a** (entry 3), it is noteworthy that all the reactions proceeded at rt in satisfactory yields (>90%). Thus, as a second step, removal of the NAPOM group from **1a**−**6a** was conducted with DDQ in an 18:1 mixture of CH_2Cl_2 and phosphate buffered water (pH 7.0) at rt. Compounds (**1a**−**5a**) were obtained in yields of 88−100%. Removal of the NAPOM group from **6b** also proceeded smoothly to give **6c** in a yield of 94%.[10] These results indicate that the NAPOM group has

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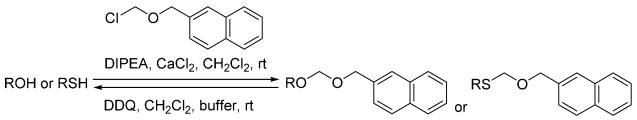
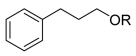
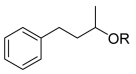
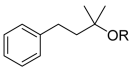
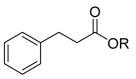
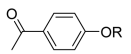
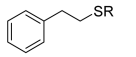
Table 1. Introduction and Removal of NAPOM Groups onto Hydroxy Groups



entry	substrate	yield / %[a] introduction[b]	removal[c]
1	 **1a**: R = H **1b**: R = NAPOM	91	98
2	 **2a**: R = H **2b**: R = NAPOM	90	96
3	 **3a**: R = H **3b**: R = NAPOM	96	91
4	 **4a**: R = H **4b**: R = NAPOM	94	88
5	 **5a**: R = H **5b**: R = NAPOM	91[d]	quant[e]
6	 **6a**: R = H **6b**: R = NAPOM **6c**: R = SCH_2CH_2Ph	88	**6c**: 94

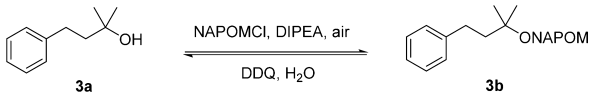
[a]Isolated yields, after silica gel column chromatography. [b]NAPOMCl (1.8 to 3 equiv), DIPEA (4 to 6 equiv), $CaCl_2$ (100 wt %), CH_2Cl_2 (subs. concn 0.1 M), rt, 6.5 to 32.5 h. [c]DDQ (1.5 equiv), CH_2Cl_2/phosphate buffered water (pH 7.0) = 18/1, rt, 2 to 3.5 h. [d]Purified by recrystallization. [e]DDQ (2.0 equiv), CH_2Cl_2/pH 7.0 buffer, rt, 22.5 h.

potential as a novel oxidatively removable member of the BOM protective groups.

To further investigate the usability of the NAPOM group, its compatibility with a number of solvents was examined. The results for the protection of **3a** and the deprotection of **3b**, conducted in various solvents, in the absence of $CaCl_2$ and exposed to air, are shown in Table 2. For the introduction of the NAPOM group, in all the solvents tested, the reactions proceeded in moderate (77% in hexane, 78% in CH_3CN, 72% in DMSO, 82% in DMF, 83% in methyl-*tert*-butyl ether (MTBE), and 85% in THF) to excellent (92% in AcOEt, 93% in toluene, and 97% in CH_2Cl_2) yields. For the deprotection with DDQ, the reaction also accepted many solvents such as CH_2Cl_2 (91%), AcOEt (97%), hexane (87%), toluene (86%), CH_3CN (98%), and MTBE (99%), although relatively polar solvents were less favored (25% in THF, 31% in DMF, and 63% in DMSO). The reaction's compatibility with atmospheric moisture, air, and a broad choice of solvents could be favorable not only in academic but also in industrial contexts.

We next turned our attention to the challenging introduction of the NAPOM group onto sensitive substrates. 1,2-Diols are known to give irregular results during protection and deprotection. Of these, monoacylated 1,2-diols are notorious for undergoing acyl migration under both acidic and basic conditions. To the best of our knowledge, clean introduction of the BOM and MOM group onto 2-acetoxy-1-ols has never

Table 2. Compatibility with Solvents



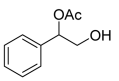
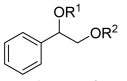
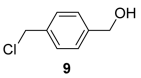
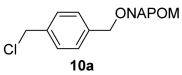
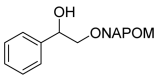
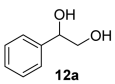
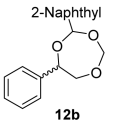
3a **3b**

	introduction		removal	
solvent	reaction time/h	yield/%[a]	reaction time/h	yield/%
hexane	50	77	15	87[c]
toluene	15.5	93	11.5	86[c]
MTBE	109	83	109	99[c]
CH_2Cl_2	39	97	2	91[b]
AcOEt	50	92	17	97[c]
THF	109	85	109	25[c]
CH_3CN	109	78	17.5	98[c]
DMF	109	82	109	31[c]
DMSO	109	72	109	63[c]

[a]3 equiv of NAPOMCl and 6 equiv of DIPEA were used. [b]1.5 equiv of DDQ were used. [c]2.5 equiv of DDQ were used.

been reported to date. First, the introduction of the NAPOM group onto monoacetylated diol **7** was attempted under the conventional conditions using DIPEA (entry 1 of Table 3).

Table 3. Introduction and Removal of NAPOM Group on Sensitive Alcohols

entry	substrate	reagents	product	yield / % a	b
1	 **7**	NAPOMCl DIPEA	 **8a**: R^1 = Ac, R^2 = NAPOM **8b**: R^1 = NAPOM, R^2 = Ac	47[a]	19[a]
2	**7**	NAPOMCl TBAI 2,6-lutidine	**8a**, **8b**	89	3
3	 **9**	NAPOMCl 2,6-lutidine	 **10a**	75	
4	 **11**	DDQ pH 7.0 buffer	 **12a**  **12b**	27	51
5	**11**	DDQ, H_2O; then MeOH	**12a**, **12b**	90	N.D.

[a]Inseparable. Yield was calculated from ^{1}H NMR spectrum of the mixture.

Despite the mild basicity and temperature, acyl migration occurred to give a mixture of the desired product **8a** (47%) and the migrated product **8b** (19%) as expected.[11] After considerable experimentation,[12] we finally found that the treatment of **7** with NAPOMCl in the presence of 2,6-lutidine and TBAI at rt (entry 2) furnished the desired compound **8a** in good yield (89%), with little migration product **8b** (3%). The method using 2,6-lutidine was also effective for the protection of **9** (giving **10a** in 75% yield, entry 3), an alcohol possessing a highly reactive benzyl chloride moiety, while a conventional mild method using Ag_2O and alkyl halides was difficult to apply.

Another task was the deprotection of the mono-NAPOM protected diol **11** (entry 4). Attempted deprotection of **11** with

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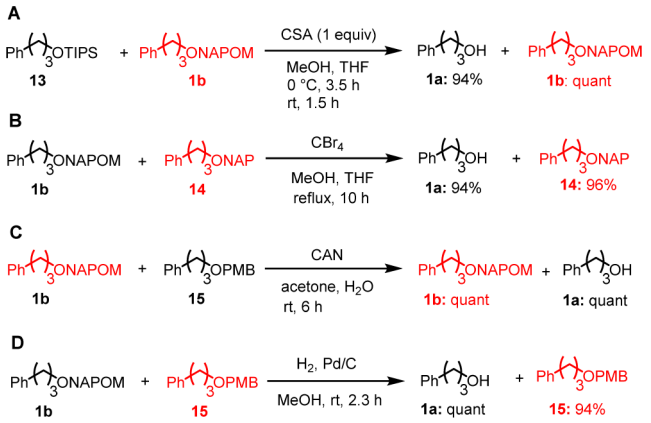
DDQ in pH. 7.0 buffer resulted in the formation of the cyclic acetal **12b** as the main product (51%) with concomitant formation of the desired diol **12a** (27%). In order to accelerate the *in situ* acidic hydrolysis of **12b** to **12a**, we examined the reaction in nonbuffered water (entry 5). Although TLC revealed the presence of more **12a** than in the previous experiment, the reaction was incomplete with remaining **12b**. However, addition of MeOH, which might act as a mediator of H^+ between the CH_2Cl_2 and H_2O phases, proved to be a solution to this problem, affording the desired diol **12a** in 90% yield.

Having established the mild introduction and robust removal methods, the characteristics and conditions of selective removal of NAPOM were investigated (Scheme 1). In acidic media, the

Scheme 1. Selective Removal[a]



[a]1:1 (mol/mol) mixture of substrates was used. For each entry, compounds whose protecting groups remained untouched are highlighted in red.

NAPOM group was found to be more stable than the triisopropylsilyl (TIPS) group, which allows the CSA-mediated selective removal of TIPS (**13**) in the presence of NAPOM ether **1b** (quantitative recovery) (Scheme 1A).[13] The difference in stability in acidic conditions also allows the selective removal of NAPOM (**1b**) in the presence of NAP (**14**, 96% recovery) by treatment with CBr_4 in refluxing MeOH (Scheme 1B).[14] On the other hand, selective removal of PMB (**15**) in the presence of the NAPOM group (**1b**, quantitative recovery) was readily achieved via treatment with CAN (Scheme 1C).[15,16] In contrast, the opposite selectivity appeared when a mixture of NAPOM- and PMB-protected compounds (**1b** and **15**) were subjected to hydrogenolysis; i.e., the NAPOM group was selectively cleaved in the presence of PMB (94% recovery), by treatment with Pd/C under a hydrogen atmosphere (1 atm) (Scheme 1D).[17]

In this paper, we have reported the development of NAPOM, a novel group of the BOM family, for the protection of hydroxy groups.[18] The advantages of the NAPOM group, i.e. (i) storability of NAPOMCl, (ii) mild introduction using 2,6-lutidine without triggering acyl migration, (iii) selective removal in the presence of NAP and PMB, (iv) compatibility with removal conditions for PMB and PMBOM, and (v) easy handling without the need for protection from atmospheric moisture and air, will facilitate organic syntheses (e.g., carbohydrates) by suggesting novel routes to the target molecules. The total synthesis of natural products using the NAPOM group is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, spectral data, and ^1H and ^{13}C NMR charts of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01408.

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Notes

The authors declare the following competing financial interest(s): A patent, regarding NAPOMCl-utilization for the protection of alcohols and thiols, is pending (Kyushu University. Japanese Patent Application No. 2014-206408, October 7, 2014).

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(3) Iversen, T.; Bundle, K. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240−1241.
(4) Many Lewis acids are also used.
(5) Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125−5128.
(6) PMBOMCl was prepared by the treatment of $PMBOCH_2SMe$ with SO_2Cl_2 at −78 °C; see: Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762−763. Subsequent hydrogenolytic deprotections of freshly prepared PMBOM ethers often resulted in failure, probably because a traceless amount of sulfur-containing species was contaminated.
(7) Stefan, E.; Taylor, R. E. *Org. Lett.* **2012**, *14*, 3490−3493. In this paper, NAPOM ether was prepared but immediately converted to the corresponding NAP ether, via an original rearrangement reaction. The usage of NAPOM as a protecting group has never been reported.
(8) NAPOMCl is storable at 4 °C for several months (1-month-storage at 4 °C caused 13% decrease of NAPOMCl), although it decomposed at rt ($t_{1/2}$ at rt is ca. 10 days).
(9) Addition of $CaCl_2$, as a neutral drying agent, is not absolutely necessary but effectively decreases the amount of NAPOMCl required for completing the reaction, probably by removing the moisture that destroys the NAPOMCl.
(10) Although the generated thiol **6a** automatically dimerized, forming a disulfide bond to give **6c**, reductions of alkyl disulfides to thiols are known in the literature (for example using LiCl, $NaBH_4$, THF). See: Rajaram, S.; Chary, K. P.; Iyengar, D. S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2001**, *40B*, 622−624.
(11) The reaction was not clean, leading to a poor mass balance.
(12) For example, use of DMAP as a base caused acyl migration.
(13) Although the NAPOM group was more stable in acidic conditions than TBDPS, attempted removal of TBDPS with complete recovery of NAPOM failed. Treatment of a 1:1 mixture of the

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NAPOM and TBDPS ethers with CSA (1 equiv) in MeOH/THF (5:1) for 4 h resulted in the recovery of the NAPOM ether in 68% yield with full consumption of TBDPS ether.
(14) Lee, A. S.-Y.; Hu, Y.-J.; Chu, S.-F. *Tetrahedron* **2001**, *57*, 2121−2126. The NAPOM group was as stable as the PMB group in protic acids (data not shown).
(15) For the selective removal of the PMB group in the presence of the NAP group, see: Wright, J. A.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **2001**, *42*, 4033−4036.
(16) In addition, as expected, NAPOM could be selectively removed in the presence of the BOM group (91% recovery) with DDQ (1.5 equiv) at rt, but conditions to remove BOM in the presence of NAPOM have not yet been identified.
(17) Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172−4173.
(18) Patent pending (Kyushu University. Japanese Patent Application No. 2014-206408, October 7, 2014).

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