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1-Naphthylmethyl and 1-naphthylmethoxymethyl protecting groups: New members of the benzyl- and benzyloxymethyl-type family

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ABSTRACT

1-Naphthylmethyl (NAP^{I}) and 1-naphthylmethoxymethyl (NAPOM^{I}) protecting groups were developed as new members of the benzyl- and benzyloxymethyl-type family. NAP^{I} and NAPOM^{I} can be introduced under conventional conditions, such as NAP^{I}Br/NaH/room temperature (rt), or NAPOM^{I}Cl/*i*-Pr$_2$EtN/rt. They can also be removed under conventional conditions, e.g., by dichlorodicyanobenzoquinone (DDQ)- or ceric ammonium nitrate (CAN)-mediated oxidation, or by hydrogenolysis. The specific advantages of these new protecting groups are: i) a less costly synthesis of NAPOM^{I}Cl compared to NAPOM^{II}Cl, ii) the possibility to remove NAPOM^{II} selectively in the presence of NAPOM^{I} by DDQ-mediated oxidation, and iii) the compatibility with strong acids even in the presence of hard nucleophiles.

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As the judicious selection of protecting groups is one of the most important factors for the successful synthesis of complex molecules with several functional groups, numerous protecting groups have been developed to date.[1] For the protection of hydroxy groups, benzyl-type protecting groups such as benzyl (Bn), *p*-methoxybenzyl (PMB), and 2-naphthylmethyl (NAP) groups are especially popular, as they are relatively stable under acidic and basic conditions, and as they can be removed under neutral conditions via Pd-catalyzed hydrogenolysis. In addition, PMB and NAP can also be removed by treatment with oxidants such as dichlorodicyanobenzoquinone (DDQ) or ceric ammonium nitrate (CAN). The introduction of benzyl-type protecting groups is usually achieved under strongly acidic (e.g., BnOC(NH)CCl$_3$ or TfOH)[2] or basic (e.g., NaH/BnBr/DMF or *i*-Pr$_2$EtN/BnBr/neat/150 °C)[3] conditions.[4] Accordingly, benzyloxymethyl-type groups, such as benzyloxymethyl (BOM), and *p*-methoxybenzyloxymethyl (PMBOM) groups are highly useful for the protection of acid- and/or base-sensitive compounds, as these protecting groups can be installed under weakly basic conditions (e.g. BOMCl/*i*-Pr$_2$EtN/rt). During our studies on protecting groups for the synthesis of natural products, we have recently developed the 2-naphthylmethoxymethyl (NAPOM)[5,6] group, which can be selectively removed in the presence of other Bn- or BOM-type protecting groups such as PMB, NAP, or BOM. Curiously, 1-naphthylmethyl (NAP^{I})[7] and 1-naphthylmethoxymethyl (NAPOM^{I}) groups, which are regioisomers of NAP^{II} and NAPOM^{II},[8] have not yet found widespread applications, despite the potential utility of their characteristic features and the lower costs relative to NAP^{II} and NAPOM^{II}. Herein, we report NAP^{I} and NAPOM^{I} as new members of the naphthalene-based protecting group family to increase the pool of available protecting groups for the synthesis of complex molecules, and we demonstrate their unique and highly useful selective removal.

Initially, we examined the protection/deprotection of various alcohols with NAP^{I} (Table 1). For that purpose, alcohols were treated with NAP^{I}Br in the presence of NaH in DMF at rt (entries 1–3). For primary (**1a**) and secondary alcohols (**2a**), the reactions proceeded smoothly to afford the corresponding NAP^{I} ethers **1b** (93%) and **2b** (88%) in good yields. As is often the case with tertiary alcohols such as **1c**, the introduction of NAP^{I} stopped prematurely at rt, to furnish the protected ether **3b** in 58% yield. In a second step, we attempted to remove the NAP^{I} group from **1b**–**3b** via oxidative (DDQ, CH_2Cl_2/H_2O = 4/1, rt) or reductive (1 atm H_2, Pd/C, MeOH, rt) conditions. As a result, the free alcohols **1a**–**3a** were obtained in high yields (97–100%). These results demonstrate the potential of the NAP^{I} group as a novel member of the Bn-type family protecting groups that can be removed oxidatively.

With this encouraging result on NAP^{I} in hand, we turned our attention to the NAPOM^{I} group. The synthesis of NAPOM^{I}Cl was

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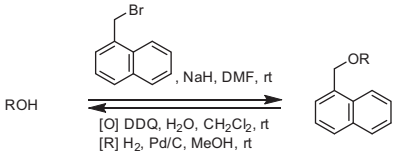
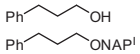
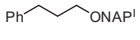
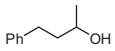
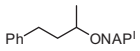
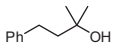
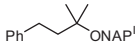
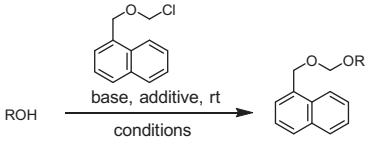
Table 1
Protection and deprotection of alcoholic hydroxy groups with NAP[I].

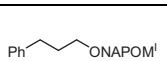
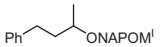
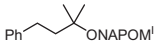
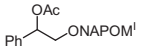
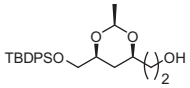
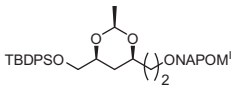


Entry	Substrate and product	Yield/%[a]		
		Introduction[b]	Removal	
			[O][c]	[R][d]
1	**1a**: 	93	98	97
	1b: 			
2	**2a**: 	88	Quant	99
	2b: 			
3	**3a**: 	58	Quant	97
	3b: 			

[a] Isolated yields after column chromatography on silica gel.
[b] NAP[I]Br (1.1 equiv), NaH (1.5 equiv), DMF ([substrate] = 1.0 M), rt, 6–26 h; reactions were monitored by TLC and quenched upon completion or stopping.
[c] DDQ (3 equiv), CH_2Cl_2/H_2O = 4/1, rt, 1.5–6.5 h.
[d] H_2 (1 atm), Pd/C (5 mol%), rt, 1.0–1.7 h.

Table 2
Protection of alcoholic hydroxy groups with NAPOM[I].



Entry	Substrate (**1a**–**6a**) and product (**1c**–**6c**)	Reagents[a]	Solvent[b]	Time/h	Yield/%[c]
1	**1a** **1c**: 	NAPOM[I]Cl *i*-Pr_2EtN	CH_2Cl_2	7.4	Quant
2	**2a** **2c**: 	NAPOM[I]Cl *i*-Pr_2EtN	CH_2Cl_2	16	90
3	**3a** **3c**: 	NAPOM[I]Cl *i*-Pr_2EtN	CH_2Cl_2	19	96
4	**3a** **3c**	NAPOM[I]Cl *i*-Pr_2EtN	Toluene	6	94
5	**4a**:  **4c**: 	NAPOM[I]Cl[d] 2,6-lutidine TBAI	CH_2Cl_2	24.5	82
6	**5a**:  **5c**: 	NAPOM[I]Cl *i*-Pr_2EtN	CH_2Cl_2	19	72
7	**6a**:  **6c**: 	NAPOM[I]Cl *i*-Pr_2EtN	CH_2Cl_2	49.5	74

[a] NAPOM[I]Cl (2–6 equiv), *i*-Pr_2EtN (4–12 equiv).
[b] [Substrate] = 0.1–0.5 M.
[c] Isolated yields after column chromatography on silica gel.
[d] NAPOM[I]Cl (6 equiv), 2,6-lutidine (12 equiv), and TBAI (0.5 equiv).

successfully achieved following a procedure similar to that of NAPOM[II]Cl, i.e., a mixture of 1-naphthylmethyl alcohol and paraformaldehyde was treated with gaseous HCl in pentane at −20 °C,[9] which furnished NAPOM[I]Cl in 85% yield.[10] It is noteworthy that 1-naphthylmethyl alcohol is substantially cheaper than 2-naphthylmethyl alcohol, which is required for the preparation of NAPOM[II]Cl.

Subsequently, the protection of alcoholic hydroxy groups with NAPOM[I] was examined (Table 2). A conventional treatment of primary, secondary, or tertiary alcohols (**1a**–**3a**, entries 1–3) with NAPOM[I]Cl and *i*-Pr_2EtN in CH_2Cl_2 at rt, furnished NAPOM[I] ethers **1c**-**3c** in good yields (90–100%). Although the required reaction time is different for primary and tertiary alcohols, a selective installation of the NAPOM[I] group in primary alcohol **1a** in the presence of tertiary alcohol **3a** was not possible under the applied reaction conditions. On the other hand, the reaction time for tertiary alcohol **3a** was shortened in toluene (entry 4), which emerged as one of the best solvents for these reactions[5] without affecting the yield of **3c** (94%). We also attempted to use NAPOM[I] to protect the hydroxy group of a 2-acetoxy-1-ol system (**4a**), whose acetyl group easily migrates under slightly acidic or basic conditions (entry 5). Although acyl migration actually occurred when *i*-Pr_2EtN was used as a base, the use of 2,6-lutidine prevented this unwanted side reaction: Treatment of **4a** with NAPOM[I]Cl, 2,6-lutidine, and a catalytic amount of tetrabutyl ammonium iodide (TBAI) in CH_2Cl_2 at rt furnished the desired NAPOM[I] ether (**4c**) in 82% yield. Ester (entry 5), olefin (entry 6), silyl ether and acetal (entry 7) moieties remained unaffected under the applied conditions to install NAPOM[I] to afford **5c** (72%) and **6c** (74%) from **5a** and **6a**,[11] respectively.

Then, we turned our attention to the removal of the NAPOM[I] group (Table 3). Under oxidative conditions using DDQ, NAPOM[I] ethers **1c**-**3c** proved to be unexpectedly resistant, which stands in contrast to the behavior of NAPOM[II].

The successful removal of NAPOM[I] (entries 1, 4, and 7) required an increased amount of DDQ (3 equiv) in combination with elevated temperatures (reflux), while NAPOM[II] can be removed smoothly using only 1.5 equiv of DDQ at rt. Although the yield of **3a** (99%) was satisfactory, those of **1a** (64%) and **2a** (86%) were not, due to the generation of byproducts, which probably formed on account of the harsh conditions. Therefore, we also examined the milder oxidant CAN (entries 2, 5, and 8). As expected, the yields improved in all cases (83, 88, and 100%, respectively), although prolonged reaction times were required. The reason why NAPOM[I] is more tolerant toward oxidation than NAPOM[II] remains unclear at this point.

Before our investigations, and based on the conventional electronic theory in organic chemistry, we expected that NAPOM[I] should be more reactive toward oxidants, given that cationic intermediate **7** should be more stable than cation **8** on account of the resonance effect (Chart 1A). However, the experimental results did not match our expectations. Interestingly, the oxidation poten-

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