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2-(Prenyloxymethyl)benzoyl (POMB) as a new temporary protecting group for alcohols

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Abstract—The 2-(prenyloxymethyl)benzoyl (POMB) group was introduced in high yields to hydroxyl functions using the crystalline reagent, 2-(prenyloxymethyl)benzoic acid, in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). 2-(Prenyloxymethyl)benzoic acid is readily available, in two steps, from phthalide in 65% overall yield. The POMB group can be cleaved, in two steps, by treatment with 2,3-dichloro-5,6-dicyanoquinone (DDQ) followed by intramolecular lactonisation of the resulting hydroxy ester induced by a catalytic amount of $Yb(OTf)_3 \cdot H_2O$. The reaction conditions are compatible with the presence of a number of protecting groups such as isopropylidene, benzyl, acetyl, chloroacetyl, benzoyl, levulinoyl, Fmoc and Boc groups.

The hydroxyl group is one of the most important functional groups present in the natural products. Although over 150 hydroxyl protecting groups have been reported, few have found wide applications.[1] Novel hydroxyl protection and new cleavage techniques for existing protecting groups are thus required as molecular targets increase in complexity and new fields such as supported-oligosaccharide synthesis emerge.[2] Among the new principle developed for the deprotection of alcohols is the assisted cleavage. These classes of protecting groups contains an auxiliary group, that initially exists in a chemically stable form and can be converted to a reactive nucleophile that facilitates the deprotection via an intramolecular reaction.[3] Ester protecting groups designed in this way can be used to liberate hydroxyl groups under mild conditions that usually do not affect common esters such as acetates or benzoates.[4] Among esters, which have been designed according to this principle are the *O*-substituted 2-(hydroxymethyl)benzoyl groups: 2-(isopropyl or methylthiomethoxymethyl)benzoyl (respectively PTMT[5] and MTMT[6]) and 2-(chloroacetoxymethyl)benzoyl (CAMB).[7]

The deblocking process of these protecting groups involves the unmasking of the hydroxyl auxiliary function ($Hg(ClO_4)_2$, base, THF–H_2O for the PTMT and MTMT groups; thiourea at 50 °C for 24–48 h for the CAMB group) followed by base-catalysed lactonisation with formation of the deblocked alcohol and phthalide.[5–7] The main drawbacks of these 2-substituted benzoates are: (1) for PTMT and MTMT groups, the high cost and toxicity of the Hg(II) salt used for the deprotection and for the MTMT group, the MTM deprotection step is for some substrates very sluggish;[5] (2) for the CAMB group, the deprotection of the chloroacetoxy group using thiourea is rather slow necessitating prolonged heating, which may cause side reactions[8] or incomplete deprotection.[7]

In relation with an ongoing project aimed at developing the uses of the prenyl group in the protection of alcohol and amine functions,[9,10] we report, in this letter, a new hydroxyl protecting group, a new derivative of the 2-(hydroxymethyl)benzoyl group namely 2-(prenyloxymethyl)benzoyl (POMB) group, which can be selectively removed under mild conditions by the couple DDQ/$Yb(OTf)_3$ (Scheme 1).

The protecting agent, 2-(prenyloxymethyl)benzoic acid (POMBOH) **1** was easily prepared according to the procedure developed for the synthesis of MTMTOH.[6] After saponification of the phthalide by

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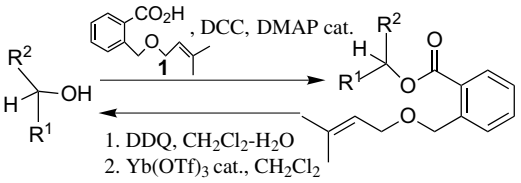
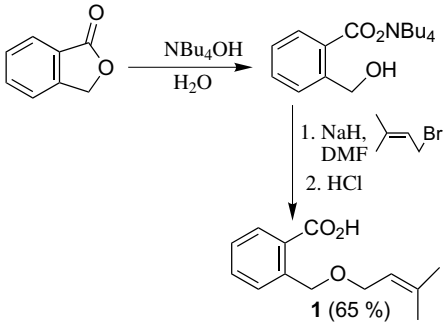


Scheme 1.

tetra-*N*-butylammonium hydroxide, the resulting oily ammonium salt was dissolved in DMF and successively treated with NaH and prenyl bromide to afford pure POMBOH **1** in 65% yield, after acidification and recrystallisation in hexane (Scheme 2).[11]



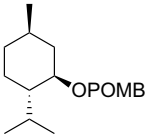
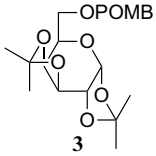
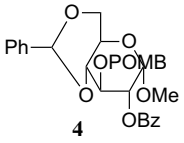
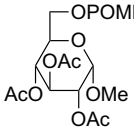
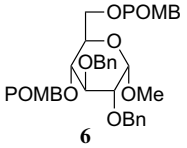
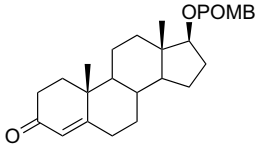
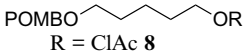
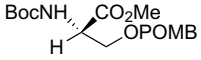
Scheme 2.

Diversely functionalised alcohols were esterified with POMBOH in CH_2Cl_2 at room temperature, in the presence of DCC and DMAP,[12] to furnish POMB esters **2**–**11** in excellent yields (90–97%).[13,14] We next examined the deprotection of the POMB group on the 2-substituted benzoates **2**–**11** with DDQ in CH_2Cl_2–H_2O, which cleaved the prenyl ether group followed by lactonisation of the resulting hydroxy ester with $Yb(OTf)_3{\cdot}H_2O$[15] (Table 1).[16] It is noteworthy that for substrates **3**–**5** and **8**–**10**, only 2 mol% of the catalyst (10 mol% for the other substrates) was necessary for the lactonisation to proceed at room temperature and at a reasonable rate (3 h).

As seen in Table 1, the reaction conditions for the POM group cleavage are compatible with a number of protecting groups such as isopropylidene, benzyl, acetyl, benzoyl, Boc groups (entries 2, 3, 4, 5, 10) but not with the benzylidene group, which was partially cleaved by $Yb(OTf)_3$ (entry 3). In the presence of $Yb(OTf)_3$, methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside, resulting from the cleavage of the POMB group of **5**, was partially transformed to methyl 2,3,6-tri-*O*-acetyl-α-D-glucopyranoside obtained in 8% yield, via acetyl migration from 4-to-6 position (entry 4).[17] Temporary protecting groups such as ClAc, Lev and Fmoc groups, which are used in the orthogonal sets of protecting groups in carbohydrate chemistry,[18] were left unscathed (entries 7–9).

In conclusion, the 2-(prenyloxymethyl)benzoyl group has been developed as a new protection for alcohols, which can be installed in high yield and cleaved selectively in the presence of other alcohol protecting groups.

Table 1. Deprotection of POMbenzoates **2**–**11** with DDQ/$Yb(OTf)_3$[a]

Entry	Substrate	Yield (%)
1	 **2**	92
2	 **3**	86
3	 **4**	60
4	 **5**	79
5	 **6**	75
6	 **7**	87
7	 R = ClAc **8**	90
8	R = Lev **9**	88
9	R = Fmoc **10**	91
10	 **11**	85

[a] For the deprenylation step, 1.5 equiv of DDQ was used for all substrates except for the di-POMB derivative **6** (3 equiv) and the reaction time was 6 h.

Considering these attributes, the 2-(prenyloxymethyl)benzoyl group may find valuable and versatile use in synthetic organic chemistry.

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11. *Preparation of 2-(prenyloxymethyl)benzoic acid **1** from phthalide*. A mixture of phthalide (4 g, 0.0298 mol) and tetra-*N*-butylammonium hydroxide in water (40% w/v, 20 mL, 0.031 mol) was heated at reflux for 90 min. The clear solution was cooled down, extracted with CH_2Cl_2 (3×40 mL) and the combined organic phases were washed with water (10 mL). The organic phase was dried (Na_2SO_4) and concentrated. The oily residue was dried under high vacuum at room temperature. To a solution of the ammonium salt (11.73 g) in DMF (40 mL), cooled to 0 °C, was added by portions NaH (60% dispersion in mineral oil, 3.6 g, 3 equiv). The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction mixture was cooled (0 °C) and prenyl bromide (4.2 mL, 1.2 equiv) was added dropwise. The mixture was stirred at room temperature for 4 h, cooled (0 °C) and MeOH was carefully added followed by H_2O (140 mL). The solution was extracted with ether (3×40 mL). To the well-stirred aqueous phase, cooled to 0 °C, was added dropwise 2 N HCl solution until pH 2 and the resulting suspension was extracted with ether (2×125 mL).The combined organic phases were dried (Na_2SO_4) and concentrated. Crystallisation of the residue in hexane gave **1** (4.3 g; 65% yield) as colourless crystals, mp 90–92 °C. IR (KBr): 1680 cm^{-1}. ^1H NMR: 1.70 (s, 3H, Me), 1.78 (s, 3H, Me), 4.13 (d, 2H, $J = 6.95$ Hz, C*H*$_2$–CH=C), 4.91 (s, 2H, C*H*$_2$Ar), 5.46 (br t, 1H, $J = 7$ Hz, C*H*=CMe$_2$), 7.4 (t, 1H, $J = 7.9$ Hz, Ar), 7.58 (t, 1H, $J = 7.8$ Hz, Ar), 7.68 (d, 1H, $J = 8$ Hz, Ar), 8.09 (d, 1H, $J = 7.8$ Hz, Ar), 9.7 (br s, 1H, CO_2H). ^{13}C NMR: 18.1, 25.9, 67.4, 70.2, 120.8, 127.6, 127.7, 128.21, 131.7, 133.2, 137.7, 141.3, 172.2. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; O, 21.79. Found: C, 70.64; H, 7.17; O, 21.99.
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15. In our knowledge, it is the first example of the use of $Yb(OTf)_3$ as a lactonisation agent.
16. *Typical procedure for the cleavage of the POMB group*. To a stirred solution of the 6-*O*-POMB diacetone galactose **3** (0.24 g, 0.52 mmol) in a mixture CH_2Cl_2–H_2O (9:1, 6 mL) was added DDQ (0.177 g, 1.5 equiv). After stirring the reaction mixture for 6 h at room temperature, sodium bicarbonate in powder was added and the stirring was continued for 10 min. The yellow phase was separated from the black gum, which was washed twice with CH_2Cl_2.The combined phases were concentrated to a volume of about 5 mL, filtered through a pad of silica gel (7 g) and eluted with ether–petroleum ether, 3:1. The resulting mixture, which is composed mainly of the hydroxy ester, was dried under vacuum and dissolved in CH_2Cl_2 (3 mL) and $Yb(OTf)_3{\cdot}H_2O$ (6.2 mg, 0.02 equiv) was added. After stirring for 3 h at room temperature, two drops of saturated $NaHCO_3$ solution was added and the stirring was continued for 5 min. After evaporation of the reaction mixture, the residue was purified by flash chromatography on silica gel (ether–petroleum ether, 3:1) to give diacetone galactose as an oil (0.116 g, 86%). $[\alpha] -54$ (*c* 2.5, $CHCl_3$) (Lit.[19] $[\alpha] -55$ (*c* 3.5, $CHCl_3$)). Spectroscopic data are in accordance with those of an authentic sample.
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