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2-(Prenyloxymethyl)benzoyl (POMB) group: a new temporary protecting group removable by intramolecular cyclization

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Abstract—2-(Prenyloxymethyl)benzoates can be prepared from alcohols and readily available 2-(prenyloxymethyl)benzoic acid by standard acylation techniques or by Mitsunobu reaction with inversion of configuration. The POMB group can be cleaved first by oxidative removal of the prenyl group with DDQ followed by lactonization with expulsion of the alcohol catalyzed by $Yb(OTf)_3$. These reaction conditions are compatible with the presence of a large number of common protecting groups.

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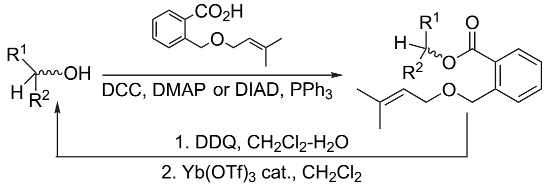
1. Introduction

The hydroxy group is one of the most present functional groups in natural products. Because it is nucleophilic, acidic, and easily oxidized in a multifunctional molecule it needs to be temporarily protected from unwanted reactions. Although over 150 hydroxy protecting groups have been reported, few have found wide applications.[1] Novel hydroxy 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 contain an inside auxiliary group that initially exists in a chemically stable form and can be converted to a reactive nucleophile facilitating the deprotection via an intramolecular reaction.[3] Ester protecting groups designed in this way can be used to liberate hydroxy 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 these four *O*-substituted 2-(hydroxymethyl)benzoyl groups: 2-(isopropyl or methylthiomethoxymethyl)benzoyl (respectively, PTMT[5] and MTMT[6]), 2-(chloroacetoxymethyl)benzoyl (CAMB)[7] and 2-[4-(methoxytrityl)thiooxymethyl]benzoyl (MOB).[8] The deblocking process of these protecting groups involves the unmasking of the hydroxy 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; iodine in pyridine–H_2O for the MOB group) followed by base-catalyzed lactonization with formation of the deblocked alcohol and phthalide.[5–8] 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 for some substrates is 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[9] or uncompleted deprotection;[7] (3) commercial unavailability of 4-MeOTrSCl used for the preparation of MOBOH.[8]

In relation with an ongoing project aimed to develop the uses of the prenyl group in the protection of alcohol and amine functions,[10,11] we have reported on a preliminary account of a new protecting group namely 2-(prenyloxymethyl)benzoyl (POMB) group selectively removable under mild conditions.[12] We now describe, in full detail, the preparation and the chemistry of POMB esters and the use of POMBOH as an *O*-nucleophile in the Mitsunobu reaction of secondary alcohols (Scheme 1).



Scheme 1.

Keywords: DDQ; Mitsunobu reaction; Prenyl ethers; Protecting groups; Ytterbium triflate.

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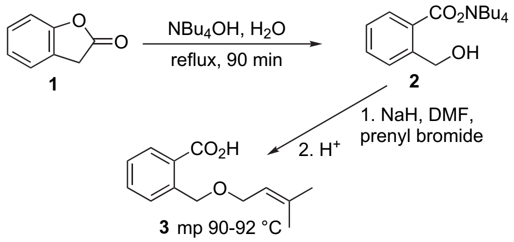
2. Results and discussion

2.1. Introduction of the 2-(prenyloxymethyl)benzoyl hydroxy protecting group

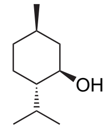
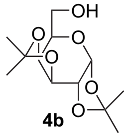
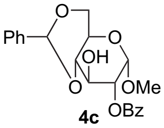
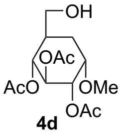
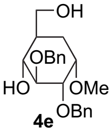
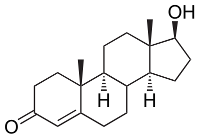
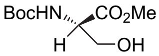
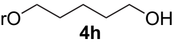
Our study commenced by the synthesis of the protecting agent 2-(prenyloxymethyl)benzoic acid (POMBOH) **3**. According to the procedure developed for the preparation of MTMOH,[6] the cheap and commercially available phthalide **1** was saponified by tetra-*N*-butylammonium hydroxide and the resulting oily salt **2**, successively treated by NaH and prenyl bromide in solution in DMF, gave crystalline POMBOH **3** in 65% yield (Scheme 2).



Scheme 2.

Diversely functionalized alcohols were esterified with 2-(prenyloxymethyl)benzoic acid at room temperature, in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP),[13] to yield esters **5a**–**5h** in excellent yields (Table 1). We next examined the efficacy of POMBOH as a partner in the Mitsunobu reaction on secondary alcohols of different steric and electronic environments. As seen in Table 2, POMBOH is a good substrate for the Mitsunobu reaction and exclusive formation of inverted esters is observed in excellent yields, even esters derived from sterically congested alcohols such as menthol (entry 3) or testosterone (entry 2). Comparison of our results with those of the literature data indicated that 2-(prenyloxymethyl)benzoic acid is notably more efficient as a oxygen nucleophile in the Mitsunobu reaction than benzoic acid (27% yield vs 85% yield in neomenthol ester (entry 3) under the same experimental conditions).[14]

Table 1. Esterification with POMBOH, DCC, and DMAP[a]

Entry	Substrate	Product	Yield (%)
1	 **4a**	**5a**	94
2	 **4b**	**5b**	92
3	 **4c**	**5c**	93
4	 **4d**	**5d**	92
5	 **4e**	**5e**	97
6	 **4f**	**5f**	90
7	 **4g**	**5g**	95
8	 **4h**	**5h**	94

For entry 5, 2-fold of each reagent was added.

[a] Reaction conditions: ROH and POMBOH (1.2 equiv) in CH_2Cl_2 at 0 °C then DCC (1.3 equiv) and DMAP (0.2 equiv) at 0 °C to rt overnight.

2.2. Cleavage of the *O*-2-(prenyloxymethyl)benzoyl protecting group

We next studied the POMB removal using menthyl POMB ester **5a** as a model substrate (Table 3). Firstly, we tested the reaction conditions (I_2 or DDQ in CH_2Cl_2–H_2O) that we developed for the cleavage of prenyl ethers.[10] Thus, in the presence of 1.5 equiv of iodine, menthol was obtained in only 52% yield (Table 3, entry 1). HI formed during the deprenylation step induced very likely the lactonization.[10c] Exposure of **5a** to 1.5 equiv of DDQ led cleanly to the formation of the deprenylated compound **6**, accompanied by 3-methylbut-2-enal (entry 2, Table 3). The known acidity of DDQ in wet solvents is too weak to catalyze the cleavage of the ester of **6** via γ-lactonization.[15] Recently, Sharma and co-workers described a mild method of O-deprenylation using a catalytic amount of $Yb(OTf)_3$ (5 mol %) in nitromethane.[16] In the presence of 20 mol % of $Yb(OTf)_3 \cdot xH_2O$ in nitromethane, the ester **5a** was uncompletely deprenylated to give a mixture of **4a** and **6** along with two unidentified by-products (entry 3). Fortunately, in dichloromethane, $Yb(OTf)_3$ (20 mol %) promoted the removal of the POMB group of **4a** and lactone formation to afford menthol in 69% yield (entry 4). In our knowledge, it is the first example of a lactonization induced by $Yb(OTf)_3$. In order to check the efficiency of $Yb(OTf)_3$ as a catalyst for lactonization, the hydroxy ester **6** was stirred in dichloromethane in its presence (10 mol %). After 3 h, TLC showed the disappearance of the starting material and the exclusive formation of menthol and phthalide. Flash chromatography of the mixture gave menthol in 96% yield. $Sc(OTf)_3$ (10 mol %) was much less effective giving a small amount of **6** along with the starting material (entry 5).

Having in hands a satisfactory two-step protocol (DDQ/$Yb(OTf)_3$) for the cleavage of the POMB group, we examined the generality of this method on diversely functionalized substrates and the results are listed in Table 4. A number of protecting groups such as acetyl, chloroacetyl,