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Development of *p*-phenylbenzyl as a new protecting group: protection and deprotection of alcohols†

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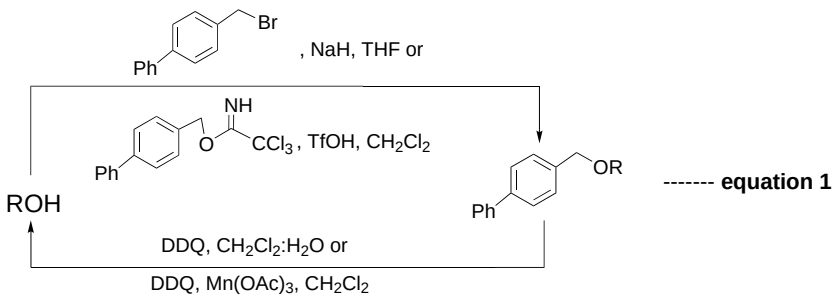
Abstract—*p*-Phenylbenzyl is developed as a new 'PMB' like protecting group. *p*-Phenylbenzyl (PPB) ethers were prepared from alcohols with PPBBr–NaH or *p*-phenylbenzyl trichloroacetimidate–TfOH and subjected to oxidative deprotection using DDQ or DDQ (10 mol%)–3 equiv. $Mn(OAc)_3$. © 2001 Elsevier Science Ltd. All rights reserved.

A wide range of blocking groups[1,2] are currently available for different functional groups, but very few of them find wide application. Identifying the correct protecting group is often decisive for the successful synthesis of a complex natural product. For a protecting group to find wide application in organic synthesis, it must fulfil certain criteria, such as being introduced and cleaved under mild conditions in high yield without affecting acid or base sensitive functionalities that are present in the molecule. Protecting groups such as benzyl, trityl,[3] diphenylmethyl,[4] *p*-methoxybenzyl[5] play a prominent role in multistep synthesis, especially in carbohydrate chemistry. In carbohydrate chemistry, a regularly encountered problem is the discriminative liberation of a specific protecting group in the presence of several others of comparable reactivity. Even though the *p*-methoxybenzyl[6] (PMB) group is a very versatile oxidation-labile[7] benzyl group, which can be removed oxidatively with DDQ, it is sensitive to acid-catalysed hydrolysis. To circumvent such a problem, development of a new 'PMB like' benzyl protecting group which can be introduced easily and deblocked oxidatively, is warranted. In continuation of our efforts[3–5,8–10] in the area of protection and deprotection in organic synthesis, herein, for the first time, we report our results on the development of *p*-phenylbenzyl (PPB) as a new group for the protection of alcohols and its removal under oxidative conditions (Eq. (1)).

The requisite *p*-phenylbenzyl bromide **1** was prepared in two steps. Accordingly, commercially available aldehyde **2** (Scheme 1) on reduction with $NaBH_4$/MeOH furnished **3** (98%), which on reaction with PBr_3 in diethyl ether gave **1** in 75% yield.

Initially alcohol **4** was treated with **1** in the presence of NaH in THF to afford the aryl ether **4a** (63%) successfully (Table 1). Similarly alcohols **5**–**8** gave the corresponding ethers **5a**–**8a** in good yields. The alcoholic function in sugar derivative **9** underwent protection to



(1)

------- **equation 1**

Keywords: *p*-phenylbenzyl bromide; *p*-phenylbenzyl (PPB) ethers; *p*-phenylbenzyl trichloroacetimidate.

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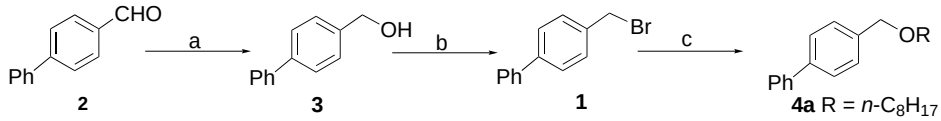


Scheme 1. *Reagents and conditions*: (a) $NaBH_4$, MeOH, rt, 1 h; (b) PBr_3, dry $(C_2H_5)_2O$, 0°C to rt, 1 h; (c) ROH, NaH, THF, 0°C to rt, 24 h.

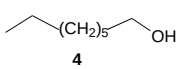
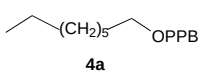
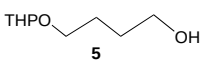
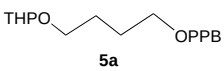
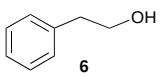
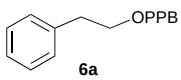
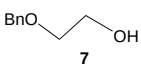
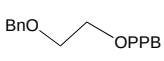
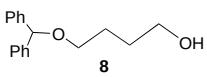
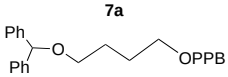
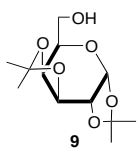
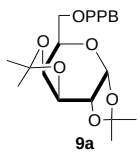
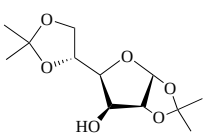
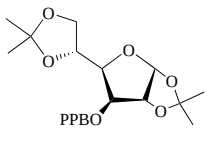
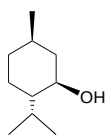
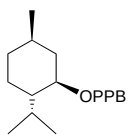
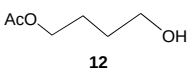
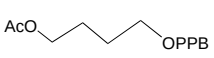
give **9a** in 68% yield. Likewise, the secondary alcoholic functions in 'diacetone glucose' **10** and menthol **11** gave the ethers **10a** (64%) and **11a** (74%), respectively. All the ethers thus prepared showed characteristic signals for the PPB group at the expected chemical shifts.

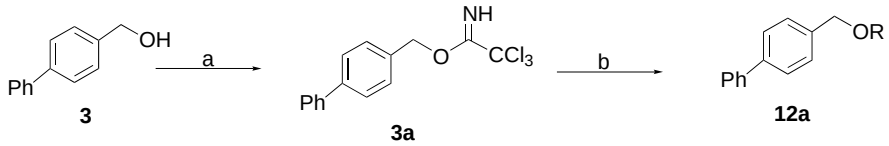
Since base sensitive groups are unstable under the above reaction conditions for the protection of alcohols, the trichloroacetimidate **3a** was envisaged as the best alternative. Accordingly, **3** (Scheme 2) was treated with NaH and CCl_3CN[11] to give **3a**, which on further reaction with **12** in the presence of a catalytic quantity of triflic acid afforded **12a** in 58% yield.

Having developed 'PPB' as an efficient benzylic protecting group for alcohols in both acidic and basic conditions, removal of the PPB group was investigated to obtain the alcohols. It was envisaged, under oxidative conditions, that the *p*-phenyl group in PPB would facilitate the formation of a benzylic carbocation. Accordingly, when **4a** was subjected to reaction with DDQ in CH_2Cl_2–H_2O (19:1) at room temperature for 3 h, alcohol **4** was obtained in 72% yield (Table 2).

Similarly, the other PPB ethers **5a**–**12a** were subjected to deprotection under the above reaction conditions to afford the respective alcohols (66–86%) in 1–5 h. In the

Table 1. Preparation of *p*-phenylbenzyl ethers

S.No.	Starting Material	Product	Time (h)	Yield (%)
1.	 **4**	 **4a**	24	63
2.	 **5**	 **5a**	24	71
3.	 **6**	 **6a**	24	65
4.	 **7**	 **7a**	12	75
5.	 **8**	 **8a**	15	65
6.	 **9**	 **9a**	24	68
7.	 **10**	 **10a**	15	64
8.	 **11**	 **11a**	26	74
9.	 **12**	 **12a**	12	58



Scheme 2. *Reagents and conditions*: (a) CCl_3CN, NaH, dry $(C_2H_5)_2O$, rt, 1 h; (b) ROH, TfOH, CH_2Cl_2, rt, 4 h.

Table 2. Oxidative removal of the *p*-phenylbenzyl protection

S. No.	Starting material	Product	Time (h)	Yield (%)
1	**4a**	**4**	3.0	72
		4[a]	17.0	69
2	**5a**	**5**	2.5	74
3	**6a**	**6**	5.0	74
4	**7a**	**7**	1.0	70
		7[a]	12.0	63
5	**8a**	**8**	2.0	68
6	**9a**	**9**	4.5	82
7	**10a**	**10**	5.0	66
8	**11a**	**11**	2.0	86
9	**12a**	**12**	2.5	66

[a] DDQ (10 mol%)–3 equiv. $Mn(OAc)_3$ was used.

case of **7a** and **8a**, the PPB group was selectively removed in the presence of both benzyl as well as diphenylmethyl groups, thus making it a very useful benzylic protecting group. All the alcohols were characterised by ^1H NMR.

Very recently, our group has reported the regeneration of DDQ using $Mn(OAc)_3$[12] as a reoxidant. Since DDQ is expensive to use in a stoichiometric quantity and the by-product quinol can create problems; in the present study, the ether **4a** was treated with DDQ (10 mol%) and 3 equiv. $Mn(OAc)_3$ to give the alcohol **4** (69%), albeit in a longer duration of time (17 h). A similar result was observed for the ether **7a**.

To evaluate the stability of the PPB group to acid hydrolysis, ether **4a** was subjected to reaction with 60% aq. AcOH at 60°C and with CF_3COOH in CH_2Cl_2 at room temperature, independently, for several hours. However, no trace of hydrolysis was observed by TLC analysis and the starting ether was recovered unchanged.

Thus, the present study discloses the development of the *p*-phenylbenzyl (PPB) group as an efficient protecting group, that can be introduced under both basic and acidic reaction conditions. Similarly, a facile removal using DDQ or cat. DDQ–$Mn(OAc)_3$, even in the presence of other benzylic groups, makes it a potentially very useful protecting group. Finally, unlike the PMB group, the stability of the PPB group towards acids is worthy of note. Thus, the PPB group due to its stability towards acids and oxidative deblocking could find wide use, particularly in carbohydrate chemistry.

Spectral data for selected compounds: ^1H NMR (200 MHz, $CDCl_3$, TMS): **4a**: δ 0.9 (t, 3H, $J=6.8$ Hz, CH_3), 1.30 (br. s, 10H), 1.60 (t, 2H, $J=6.8$ Hz), 3.45 (t, 2H, $J=6.8$ Hz, OCH_2), 4.50 (s, 2H, OCH_2Ar), 7.20–7.42 (m, 5H, ArH), 7.44–7.60 (m, 4H, ArH); EIMS: m/z 296 (M^+, 17.0%), 236 (5.2%), 167 (100%), 77 (20.3%), 42 (55.4%); **5a**: δ 1.40–1.95 (m, 10H), 3.30–3.58 (m, 4H), 3.65–3.90 (m, 2H), 4.45–4.60 (m, 3H), 7.22–7.45 (m, 5H, ArH), 7.48–7.60 (m, 4H, ArH); EIMS: m/z 255 (M^+–THP, 13.7%), 167 (61.7%), 85 (59.2%), 42 (100%); **11a**: δ 0.75 (d, 2H, $J=5.0$ Hz), 0.82–1.05 (m, 10H), 1.22–1.45 (m, 2H), 1.60–1.75 (m, 2H), 2.18–2.42 (m, 2H), 3.10–3.25 (m, 1H), 4.55 (dd, 2H, OCH_2Ar), 7.30–7.48 (m, 5H, ArH), 7.50–7.60 (m, 4H, ArH); $[\alpha]_D=-77.72$ (*c* 1.15, $CHCl_3$); EIMS: m/z 322 (M^+, 7.5%), 167 (100%), 123 (13.2%), 81 (29.3%), 42 (99.5%).

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