



Cleavage of benzyl ethers by triphenylphosphine hydrobromide

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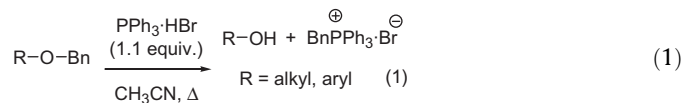
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ABSTRACT

Triphenylphosphine hydrobromide was found to cleave the benzyl ethers derived from 1°, 2° alkyl, and aryl alcohols to the corresponding alcohols and benzyltriphenylphosphonium bromide in good yields. Alkene and allyl phosphonium salts were produced from the benzyl ethers with 3° alkyl and allyl groups, respectively. These results indicate that the formation of the product is determined by the relative stability of the carbocationic intermediate. The anhydrous, stoichiometric amount of PPh₃·HBr offers a new and effective method for the deprotection of benzyl ethers.

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Protecting hydroxyl groups as benzyl ethers (Bn–OR) have been widely applied in multi-step organic synthesis. Benzyl ether is robust, relatively low cost in preparation, and orthogonal to other protective groups, making benzyl ether and its derivatives, such as *p*-methoxybenzyl ether (PMB–OR), among the most used protective groups.¹ Conventionally, the removal of the benzyl group is achieved by hydrogenolysis² (H₂, Pd/C, or Raney Nickel), reductive or oxidative cleavage (Na/ammonia and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, etc);^{3–5} however, these methods might be incompatible with unsaturated substrates and reduction/oxidation sensitive functional groups. Brønsted acid and Lewis acid based cleavage provides alternative deprotection methods when such concerns are involved. For example, trifluoromethanesulfonic acid, trifluoroacetic acid, iodotrimethylsilane, and boron trichloride have been developed along this direction.^{6,7} Recently, debenzyla-tion with the combination of chlorosulfonyl isocyanate–sodium hydroxide was reported.⁸ Although ethers are known to hydrolyze in hydrobromic acid or anhydrous hydrogen bromide,⁹ only a few examples using HBr to cleave benzyl ethers have been reported,^{10,11} probably due to the strongly acidic or aqueous reaction conditions being incompatible with other functional groups. Herein, we would like to report the deprotection of benzyl ethers using triphenylphosphine hydrobromide (PPh₃·HBr). In contrast to the volatile and flammable boron/silicon based Lewis acids, or inconvenient HBr, the salt PPh₃·HBr is a stable, white powder (mp 196 °C),¹² which makes it easy to apply with a correct quantity. Indeed, PPh₃·HBr has been used as the source of anhydrous hydrogen bromide,¹³ an alternative of sulfonic acids,¹⁴ and the precursor of phosphorus ylides.¹⁵ We found that PPh₃·HBr could also be used in the deprotection of benzyl ethers (Eq. 1) and would like to report this finding herein.



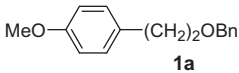
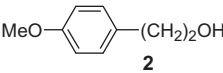
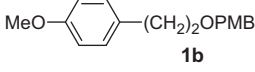
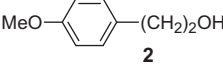
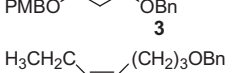
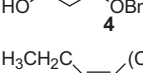
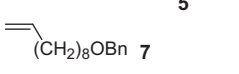
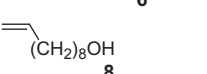
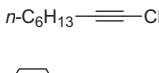
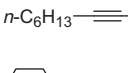
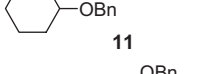
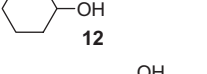
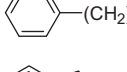
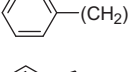
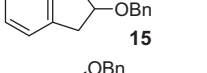
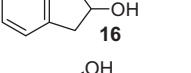


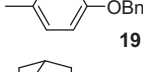
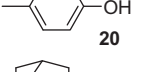
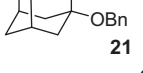
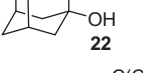
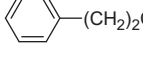
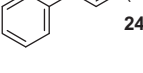
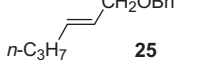
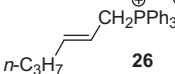
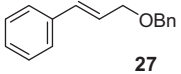
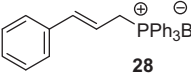
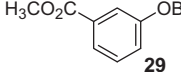
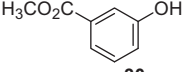
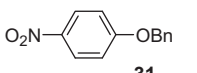
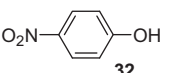
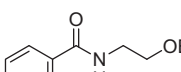
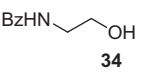
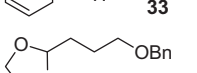
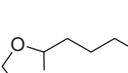
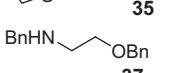
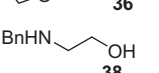
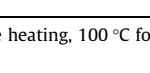
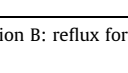
The reactions of various benzyl alkyl or aryl ethers with PPh₃·HBr were carried out in refluxing acetonitrile (Table 1).¹⁶ The insoluble by-product, benzyltriphenylphosphonium bromide, could be removed by simple filtration and the deprotected alcohols were harvested after the removal of the solvent. Later, we shortened the reaction time to 30 min by elevating the reaction temperature to 100 °C under a microwave-assisted heating condition. This protocol also removed *p*-methoxybenzyl (PMB) group (entry 2). Indeed, we found that the PMB ether is more susceptible to PPh₃·HBr than the benzyl ether and the selective deprotection was achieved (entry 3). All the primary, secondary, and aryl alcohol-derived benzyl ethers were deprotected successfully (entries 4–11). Internal olefin and alkynyl groups remained intact under the reaction condition (entries 4 and 6) but partial hydrobromination was observed for the terminal olefin (entry 5). Although 1-admantanol (**22**) was produced from the ether **21** (entry 12), the tertiary alcohol-derived benzyl ether **23** gave the elimination product **24** (entry 13). Allyl and cinnamyl ethers, **25** and **27** gave only the corresponding phosphonium bromides **26** and **28**, rather than the allyl and cinnamyl alcohols (entries 14 and 15). These results are consistent with the triphenylphosphine attaching to the ether substituents (R–O–Bn) with the more carbocationic character (Scheme 1). The formation of tertiary or allyl alcohols was not observed because the corresponding carbocations have better or parallel stability compared to the benzyl group.^{18,19}

The anhydrous condition and stoichiometric amount of HBr offer some advantages that hydrobromic acid and gaseous HBr cannot provide. For example, debenzylations were achieved in the presence of the ester, amide, and 1,3-dioxolane functional groups (entries 16, 18–19). The oxidation/reduction sensitive functional groups, such as alkene, alkyne, and nitro are compatible with

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Table 1
Cleavage of benzylethers with PPh₃-HBr

Entry	Reactant	Product	Condition ^a	Yield ^b (%)
1	 1a	 2	A	77
			B	54
2	 1b	 2	A	88
			B	76
3	 3	 4	A	63
4	 5	 6	A	88
5	 7	 8	A	45(26) ^c
			B	63(8) ^c
6	 9	 10	A	62
7	 11	 12	A	87
8	 13	 14	A	93
9	 15	 16	A	88
10	 17	 18	A	94
11	 19	 20	A	66
12	 21	 22	A	83
13	 23	 24	A	89
14 ^d	 25	 26	A	91
15 ^d	 27	 28	A	93
16	 29	 30	A	97
17	 31	 32	A	61
18	 33	 34	A	67
			B	84
19	 35	 36	A	57 ^e
20 ^d	 37	 38	A	72
			B	66

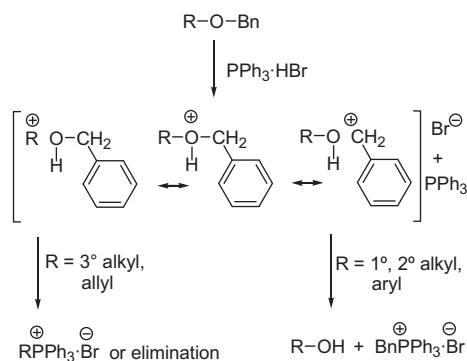
^a Condition A: microwave heating, 100 °C for 30 min in a sealed tube; condition B: reflux for 12 h.¹⁵

^b Isolated yield.

^c 9-Bromodecanol.

^d 2.1 equiv of PPh₃-HBr were used.

^e Basic, aqueous work-up was applied; Ref. 17.



Scheme 1. Proposed debenzyltion mechanism by $\text{PPh}_3\cdot\text{HBr}$.

$\text{PPh}_3\cdot\text{HBr}$ (entries 4, 6, and 17, respectively). Benzyl amine is unaffected during the removal of the benzyl ether (entry 20).

In summary, it was found that triphenylphosphine hydrobromide is a new and effective reagent for the deprotection of benzyl ethers. The studies of the reaction scope indicate that the formation of product is determined by the relative stability of the carbocationic intermediate.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures including the syntheses, ^1H NMR and ^{13}C NMR spectra for all the new compounds) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2010.09.065](https://doi.org/10.1016/j.tetlet.2010.09.065).

References and notes

- (a) Wuts, P. G. M.; Greene, T. W. In *Protective Groups in Organic Synthesis*, 4th edition; John Wiley & Sons: New York, 2007; p 102; (b) Weissman, S. A.; Zewge, D. *Tetrahedron* **2005**, *61*, 7833; (c) Jarowicki, K.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2109, and references cited therein.
- (a) Vincent, A.; Prunet, J. *Tetrahedron Lett.* **2006**, *47*, 4075; (b) Kanie, O.; Grotenbreg, G.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 4545; (c) Yoshino, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10239; (d) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021; (e) Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5397.
- Reductive cleavage: (a) Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 14355; (b) Liu, H.-J.; Yip, J.; Shia, K. S. *Tetrahedron Lett.* **1997**, *38*, 2252; (c) Schön, I. *Chem. Rev.* **1984**, *84*, 287.
- Oxidative cleavage: (a) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524; (b) Baek, S.; Jo, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, *7*, 75.
- Other debenzyltion: Hwu, J. R.; Wong, F.-F.; Huang, J.-J.; Tsay, S.-C. *J. Org. Chem.* **1997**, *62*, 4097.
- (a) Yajima, H.; Fujii, N.; Ogawa, H.; Kawatani, H. *J. Chem. Soc., Chem. Commun.* **1974**, 107; (b) Fletcher, S.; Gunning, P. T. *Tetrahedron Lett.* **2008**, *49*, 4817.
- (a) Petchmanee, T.; Ploypradith, P.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 2892; (b) Sharma, G. V. M.; Reddy, C. G.; Krishna, P. R. *J. Org. Chem.* **2003**, *68*, 4574; (c) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761; (d) Guindon, Y.; Yoakim, C.; Morton, H. E. *Tetrahedron Lett.* **1983**, *24*, 2969; (e) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.
- (a) Kim, J. D.; Han, G.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2003**, *44*, 733; (b) Rizzi, E.; Dallavalle, S.; Merlini, L.; Beretta, G. L.; Pratesib, G.; Zunino, F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4313.
- (a) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249; (b) Tiecco, M. *Synthesis* **1988**, 749.
- (a) Evans, D. A.; Scheerer, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6038; (b) Xiong, Z.; Gao, D. A.; Cogan, D. A.; Goldberg, D. R.; Hao, M.-H.; Moss, N.; Pack, E.; Pargellis, C.; Skow, D.; Trieselmann, T.; Werneburg, B.; White, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1994; (c) Hajela, S. P.; Johnson, A. R.; Xu, J.; Sunderland, C. J.; Cohen, S. M.; Caulder, D. L.; Raymond, K. N. *Inorg. Chem.* **2001**, *40*, 3208; (d) Kim, M.; Mao, Q.; Davidson, B. L.; Wiemer, D. F. *J. Med. Chem.* **2003**, *46*, 1603; (e) Leighton, P.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2385; (f) Messeri, T.; Pentassuglia, G.; Di Fabio, R. *Tetrahedron Lett.* **2001**, *42*, 3227.
- Cohen, N.; Weber, G.; Banner, B. L.; Lopresti, R. J.; Schaer, B.; Focella, A.; Zenchoff, G. B.; Chiu, A.-M.; Todaro, L.; O'Donnell, M.; Welton, A. F.; Brown, D.; Garippa, R.; Crowley, H.; Morgan, D. W. *J. Med. Chem.* **1989**, *32*, 1842.
- Meier, M. S. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 8, p 5392.
- Hercouet, A.; Le Corre, M. *Synthesis* **1988**, 157.
- Bolitt, V.; Mioskowski, C.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1988**, *29*, 4583.
- McCullough, K. J. *Tetrahedron Lett.* **1982**, *23*, 2223.
- Standard procedure for debenzyltion, condition A*: A solution of a benzyl ether (0.5 mmol), triphenylphosphine hydrobromide (0.55 mmol) in dry acetonitrile (0.5 mL) was placed in a vial (10 mL, for microwave reaction). The vial was capped and heated to 100 °C for 30 min in a microwave oven (CEM Discover). After cooling to room temperature, the suspension was diluted with EtOAc (10 mL), and filtered to remove the benzyltriphenylphosphonium bromide salt. The organic layer was concentrated under reduced pressure to give the desired product. The crude product could be further purified by flash column chromatography.
Condition B: A solution of an alkyl benzyl ether or aryl benzyl ether (0.5 mmol) in dry acetonitrile (1 mL) was added with triphenylphosphine hydrobromide (0.55 mmol). The reaction mixture was heated to reflux for 12 h. The work-up procedure was the same as the microwave-assisted condition.
- The work-up procedure for compound 36*: After cooling to rt, the reaction mixture, starting from 0.45 mmol of **35** was added with ammonium hydroxide (30%, 1 mL), and extracted with diethyl ether (10 mL \times 2). The organic layers were combined, dried over Na_2SO_4 , filtered, and concentrated. The crude product was further purified by flash column chromatography (20%, EA/hexanes) to give **36** (34 mg, 0.26 mmol, 57%).
- Smith, M. B.; March, J. In *March's Advanced Organic Chemistry*; Wiley-Interscience: New York, 2007; p 244.
- This deprotection is another example of 'push-pull' mechanism: (a) Fujii, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661; (b) Kiso, Y.; Ukawa, K.; Nakamura, S.; Ito, K.; Akita, T. *Chem. Pharm. Bull. Jpn.* **1980**, *28*, 673; (c) Yajima, H.; Fujii, N. *J. Am. Chem. Soc.* **1981**, *103*, 5867; (d) Tam, J. P.; Heath, W. F.; Merrifield, R. B. *J. Am. Chem. Soc.* **1986**, *108*, 5242. A reviewer's comment is appreciated.