A Bench-Stable Organic Salt for the Benzylation of Alcohols

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Abstract: 2-Benzyloxy-1-methylpyridinium triflate (Bn–OPT) effects the benzylation of alcohols in the absence of acidic or basic promoters. Solutions of Bn–OPT and primary, secondary, or tertiary alcohols give rise to the corresponding benzyl ethers upon mild heating. Acid scavengers are generally included in the reaction mixture. Bn–OPT is crystalline and bench-stable.

Key words: synthesis, benzyl ethers, protecting groups, alcohols

Benzyl ethers play an important role in synthetic chemistry as protecting groups for sensitive alcohol functionality.[1] Most benzyl ethers are formed using one of two standard protocols: (1) benzyl halide and base or (2) benzyl trichloroacetimidate and acid[2] (Figure 1). Herein we report a third option.

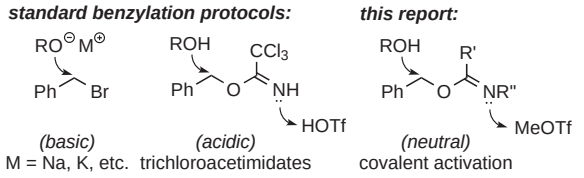
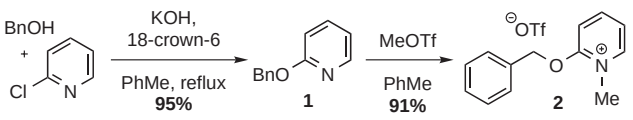


Figure 1 Synthesis of benzyl ethers from alcohols.

The need for acid or base activation limits benzylation reactions to substrates that tolerate such conditions. A preactivated benzylation reagent – that is, one that provides the ether simply upon mixing with the alcohol substrate – would be ideal. Towards this end, we envision covalent activation of an acetimidate surrogate as a means of preparing benzyl ethers under neutral conditions (Figure 1).[3–6]

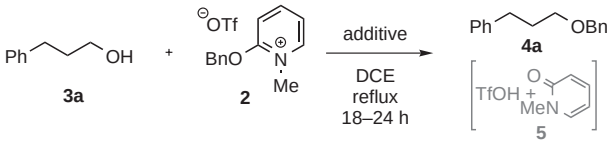


Scheme 1 Synthesis of benzyloxypyridinium triflate **2** (Bn–OPT).

This Letter describes fruitful efforts aimed at reducing this idea to practice using 2-benzyloxypyridine (**1**)[7] as the acetimidate surrogate and benzyloxypyridinium triflate **2** (Bn–OPT, Scheme 1) as the covalently activated reagent. The benzylation of alcohols using Bn–OPT is general and potentially useful. Triflate salt **2** is a white, microcrystalline solid that is typically stored in a vial at room temperature until needed.

Table 1 lists representative examples from our initial screening of the reaction between 3-phenylpropanol (**3a**) and Bn–OPT **2**. Dichloroethane (DCE), in which **2** readily dissolves, is a convenient reaction solvent. MgO may be employed as an acid scavenger, although the reasonable yield achieved in the absence of an acid scavenger suggests that it is not critical (Table 1, entry 5). The presumed by-product of the reaction, 1-methyl-2-pyridone (**5**), is highly polar, water soluble, and easy to separate from most benzyl ethers. A small amount of Bn_2O is typically formed, possibly as a consequence of adventitious moisture.

Table 1 Initial Screening of Benzylation Conditions



Entry	Additive	Equivalents of **2**	Yield[a]
1	2,6-lutidine	1.0	43% (57%)
2	Hünig's base	1.0	29% (39%)
3	K_2CO_3	1.0	68% (93%)
4	MgO	1.0	78% (93%)
5	none	1.0	53% (87%)
6	MgO	2.0	76% (85%)
7	MgO	3.0	87%

[a] Estimated by ^{1}H NMR spectroscopy. Value in parenthesis refers to calculated yield based on recovered alcohol.

The conditions described in Table 1, entry 6 [**2** (2.0 equiv), MgO] were chosen for further screening of primary, secondary, and tertiary alcohols (Table 2). Phenol **3g** reacted sluggishly (Table 2, entry 7), presumably because it is less nucleophilic than an aliphatic alcohol. The chiral ester (Table 2, entry 4) showed no evidence of epimerization, which is important due to the propensity of other benzylation protocols to epimerize labile chiral centers.[8]

As outlined above, a wide range of benzyl ethers are formed simply upon heating the alcohol substrates in the presence of **2**. The avoidance of strongly basic reaction

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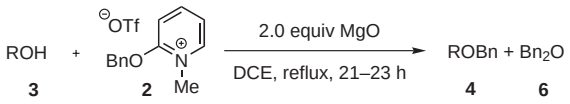
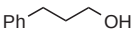
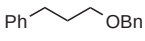
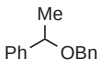
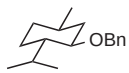
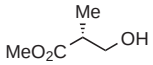
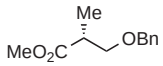
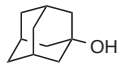
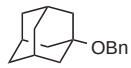
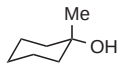
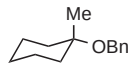
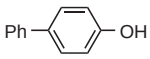
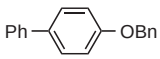
Table 2 Benzylation of Representative Alcohols

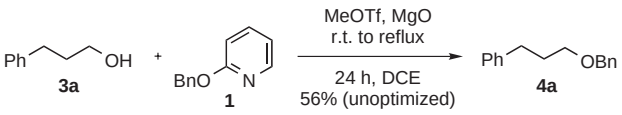


Entry	ROH **3**	ROBn **4**	Yield[a]
1	 **3a**	 **4a**	76%
2	 **3b**	 **4b**	73%
3	 **3c**	 **4c**	70%
4	 **3d**	 **4d**	72%[b]
5	 **3e**	 **4e**	84%
6	 **3f**	 **4f**	54%
7	 **3g**	 **4g**	45%[c]

[a] Estimated yield of **4** unless otherwise indicated; product and Bn_2O by-product (ca. 10% by weight) were difficult to separate by silica gel chromatography.
[b] Isolated yield of pure product, determined by chiral HPLC to be >99% ee.
[c] Alcohol **3g** was also recovered in 46% yield.

conditions permits the benzylation of chiral, epimerizable alcohols with no apparent loss of enantiomeric purity.

The active reagent, Bn–OPT **2**, is prepared by treating 2-benzyloxypyridine[7] in toluene with a slight excess of methyl triflate. The material thus obtained is analytically pure; recrystallization of **2** from THF–hexanes had no discernable effect on its properties.



Scheme 2 One-pot benzylation using in situ covalent activation of **1**.

Alternatively, in situ activation of 2-benzyloxypyridine (**1**) can be accomplished by selective methylation of **1** in the presence of an alcohol [Scheme 2, **1** (2 equiv), MgO (2 equiv), and MeOTf (2 equiv)]. This one-pot procedure eliminates the need to isolate the activate reagent.

In summary, we have disclosed initial findings on the synthesis and utility of Bn–OPT (**2**), which may in time emerge as a choice reagent for the protection of alcohols. Further optimization is in progress. The benzylation reactions cover a broad spectrum of primary, secondary, and tertiary alcohol substrates without the need for acidic or basic promoters, and the reaction mixture can be buffered using acid scavengers. Results from our ongoing development of this and related reagents will be reported in due course.

Bn–OPT (2)
MeOTf (1.05 equiv) was added to an ice-cold solution of **1**[7] in toluene (1.0 M) under argon. The ice-bath was removed and **2** precipitated from the reaction mixture. After 40 min at r.t., the volatiles were removed in vacuo to yield **2** as a white, microcrystalline solid; mp 82–86 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.8 Hz, 1 H), 8.33 (apparent t, 1 H, *J* = 8.3 Hz), 7.61 (d, *J* = 9.0 Hz, 1 H), 7.51–7.40 (m, 6 H), 5.56 (s, 2 H), 4.11 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6, 148.0, 143.8, 132.5, 129.6, 129.1, 128.5, 119.0, 112.1, 74.5, 42.0.

HRMS (ESI^+): *m*/*z* calcd for $C_{13}H_{14}NO^+$: 200.1070; found: 200.10704.

Benzylation of Alcohols Using Bn–OPT (2)
A mixture of Bn–OPT **2** (2.0 equiv), MgO (2.0 equiv), and alcohol **3** (1.0 equiv) in DCE (ca. 0.5 M) was heated in an oil bath at 83 °C for 21–23 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. Silica gel chromatography afforded **4** and small amounts of Bn_2O, the source of which is under investigation.

Acknowledgment

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References

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(2) TfOH is generally required, whereas milder acids will promote the formation of *p*-methoxybenzyl ethers; see ref. 1.
(3) Scattered literature reports provided the foundation for this work. In particular, alkoxypyridinium bromides decompose to pyridones and alkyl bromides via nucleophilic attack of the bromide ion (ref. 4), whereas alkoxypyridinium sulfonates are isolable (ref. 5). Note that Mukaiyama's reagent (ref. 6) has been employed to convert alcohols into thioesters and azides.
(4) Joshi, R. A.; Ravindranathan, T. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1984**, *23*, 260.
(5) (a) Beattie, D. E.; Crossley, R.; Dickinson, K. H.; Dover, G. M. *Eur. J. Med. Chem.* **1983**, *18*, 277. (b) See also: Kornblum, N.; Coffey, G. P. *J. Org. Chem.* **1966**, *31*, 3449.

(6) For leading references, see: (a) Hojo, K.; Yoshino, H.; Mukaiyama, T. *Chem. Lett.* **1977**, 437. (b) Hojo, K.; Kobayashi, S.; Soai, K.; Ikeda, S.; Mukaiyama, T. *Chem. Lett.* **1977**, 635.
(7) (a) Serio, A. J.; Duggan, E.; Grabowski, J. J.; Russ, W. K. *Synthesis* **1980**, 573. (b) Cherng, Y.-J. *Tetrahedron* **2002**, *58*, 4931. (c) We prepared **1** by the following procedure, which is a modification of that reported in ref. 7a: A toluene solution of benzyl alcohol (0.5 M, 1.0 equiv), 2-chloropyridine (1.2 equiv), KOH (3.2 equiv, powdered with a mortar and pestle), and 18-crown-6 (0.05 equiv) was heated at reflux for 1 h with azeotropic removal of water. Routine aqueous workup and purification on silica gel afforded **1** in 96% yield.
(8) Widmer, U. *Synthesis* **1987**, 568.