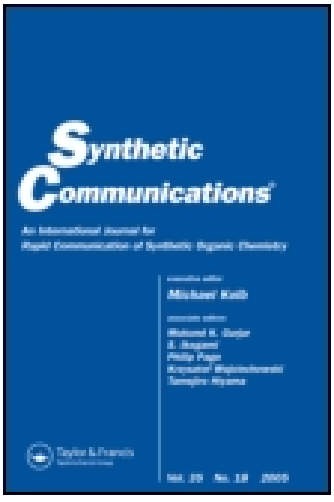

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Stable Oxypyridinium Triflate (OPT) Salts for the Synthesis of Halobenzyl Ethers

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Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida, USA

Abstract: A collection of new oxypyridinium triflate reagents (**1a–d**) for the synthesis of halobenzyl ethers from alcohols under "mix-and-heat" conditions is described. The reagents are stable organic salts that can be stored indefinitely and handled without special precautions, making them attractive for general use in organic synthesis. Halobenzylation of representative alcohols occurs in good to excellent yield.

Keywords: oxypyridinium salt, *p*-bromobenzyl, *p*-iodobenzyl, *p*-chlorobenzyl, *o*-bromobenzyl, arylmethylation

Recent reports from this laboratory describe the synthesis and reactivity of 2-benzyloxy-1-methylpyridinium triflate (benzyl-OPT, 4),[1] a stable organic salt that gives rise to benzyl ethers under relatively neutral conditions upon heating in the presence of a broad spectrum of primary and secondary alcohols [Eq. (1)]. Magnesium oxide (MgO) is typically included as the terminal acid scavenger to quench the immediate by-product of the

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This paper is dedicated to Professor Ken Goldsby (FSU) for his promotion and support of undergraduate research.

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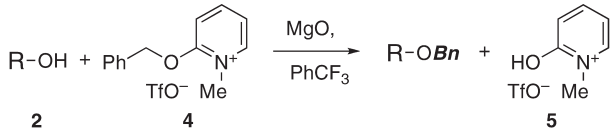
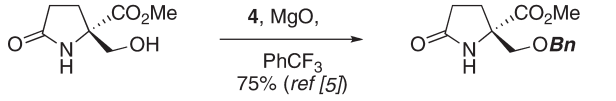
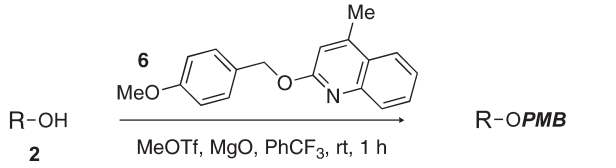
reaction, hydroxypyridinium salt **5**. Benzyl-OPT (**4**) is easy to prepare and use,[2] it is now commercially available,[3] and it has proven effective at delivering the benzyl protecting group[4] onto alcohol substrates even in difficult cases for which benzyl bromide and benzyl trichloroacetimidate were reported to be unsuitable [e.g., Eq. (2)].[5]



2 **4** **5** (1)



(2)



2 (3)

In addition to the benzyl (Bn) protecting group, many other arylmethyl ethers have been developed for the myriad protecting group needs that arise during complex organic synthetic endeavors.[4] In light of promising results in the formation of benzyl ethers, research efforts continued with an examination of related oxypyridinium triflate (OPT) salts for accessing the full complement of designer arylmethyl ethers. First to be investigated was the synthesis of *para*-methoxybenzyl (PMB) ethers, but the protocol that was optimal for making benzyl ethers did not translate into successful synthesis of PMB ethers. Significant modifications to the original strategy were required: in lieu of a pre-formed pyridinium triflate salt (cf. **4**), in situ methylation of PMBO-lepidine **6** was employed in the presence of alcohols [Eq. (3)].[6]

In contrast, halobenzyl ethers[7] — *para*-bromobenzyl (PBB), *para*-chlorobenzyl (PCB), *para*-iodobenzyl (PIB), and *ortho*-bromobenzyl (OBB) — are readily prepared using the stable OPT salts depicted in Fig. 1. This report describes the synthesis of an extended family of reagents suitable for preparing halobenzyl ethers from alcohols.

Halobenzyl ethers fill an important niche among arylmethyl protecting groups; the halide substitutent provides a convenient handle for derivatization en route to their cleavage under mild conditions, as has been described in detail previously.[7] For example, palladium-catalyzed amination technology[8] discriminates between the various halobenzyl ethers [Eq. (4)] and

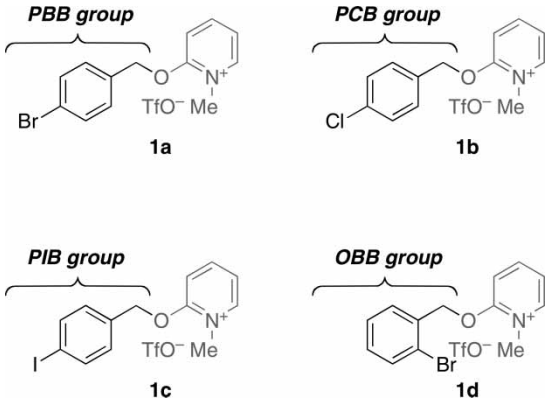
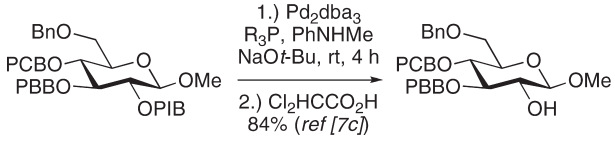


Figure 1. Oxypyridinium triflates for the synthesis of halobenzyl ethers.

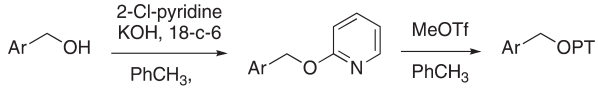
promotes their selective removal in the presence of many other common protecting groups.[7c,7f]



(4)

Methods employed for the synthesis of benzyl salt **4**[1,2] proved to be readily adaptable to the synthesis of oxypyridinium salts **1**. Arylmethyl alcohols (**7**) couple with 2-chloropyridine under basic conditions to provide pyridyl ethers **8** in excellent yield (95–99%, Table 1). Toluene solutions of **8** were then treated with methyl triflate to produce OPT salts **1**, which precipitated from the reaction mixture and were recovered in 93–96% yield by filtration and/or evaporation of the residual methyl triflate and solvent. Salts **1** were routinely stored in vials under ambient conditions without any evidence of decomposition.

Table 1. Preparation of **1a–d**, the halobenzyl-oxypyridinium salts



7 **8** **1**

Entry	Ar	Pyridyl ether	Yield of **8**	Triflate salt	Yield of **1**
1	*p*-Br-Ph	**8a**	97%	**1a**	96%
2	*p*-Cl-Ph	**8b**	96%	**1b**	95%
3	*p*-I-Ph	**8c**	99%	**1c**	96%
4	*o*-Br-Ph	**8d**	95%	**1d**	93%

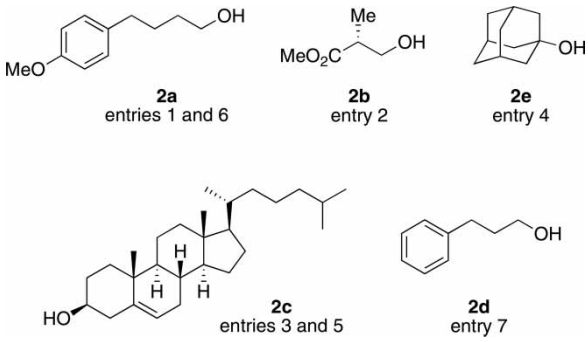
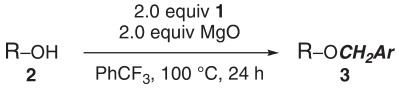


Figure 2. Alcohol substrates referenced in Table 2.

To probe the reactivity of these new reagents, halobenzylation of representative alcohols (Fig. 2) was examined under conditions similar to those previously reported for the synthesis of benzyl ethers.[1,2] As described in earlier reports, benzyl ethers form using salt **4** when reaction mixtures are heated at 80°C for 24 h. Perhaps because of the mild deactivating effect of the electronegative halides, in the present study optimal reactivity was observed at 100°C. Reaction with primary and secondary alcohols and adamantanol reliably provided halobenzyl ethers **3** in good to excellent yield (Table 2). Note that benzylation of Roche ester **2b** (cf. entry 2) fails under Williamson ether conditions[9] and that halobenzylations of anisole-derived alcohol **2a** (entries 1 and 6) proceeded smoothly despite the potential for Friedel–Crafts-type benzylation of the electron-rich arene.[10,11]

In summary, this report describes a group of reagents that are suitable for the synthesis of halobenzyl ethers. Given the special utility of diverse arylmethyl ethers, tools capable of introducing them into highly functionalized

Table 2. Synthesis of halobenzyl from alcohols



Entry	R-OH	OPT salt	Product (3)	CH_2Ar	Yield
1	**2a**	**1a**	**3aa**	PBB	89%
2	**2b**	**1a**	**3ba**	PBB	79%
3	**2c**	**1a**	**3ca**	PBB	92%
4	**2e**	**1a**	**3ea**	PBB	86%
5	**2a**	**1b**	**2cb**	PCB	93%
6	**2d**	**1c**	**3ac**	PIB	92%
7	**2a**	**1d**	**3dd**	OBB	95%

systems are valuable.[12] This nearly neutral mix-and-heat protocol for the synthesis of halobenzyl ethers will help address specific challenges in synthetic organic chemistry and promote further research into the synthetic utility of bench-stable oxypyridinium triflate salts.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300-MHz spectrometer using $CDCl_3$ or acetone-d_6 as the deuterated solvent. The chemical shifts (δ) are reported in parts per million (ppm) relative to internal TMS (0 ppm for ^{1}H NMR) or the residual $CHCl_3$ peak (7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR). The coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded using chemical ionization (CI) or electron ionization (EI) techniques. Toluene was purified by passing through a column of activated alumina. Anhydrous α,α,α-trifluorotoluene was purchased in a Sure-Seal® bottle and used as received. MgO was dried by heating at 100°C under a vacuum overnight. Neutral organic compounds were purified by flash-column chromatography using silica-gel F-254 (230–499 mesh). Yields refer to isolated material judged to be at least 95% pure by ^{1}H NMR spectroscopy.

Halobenzyloxypyridines 8 (General Procedure)

A mixture of halobenzyl alcohol **7** (1.0 equiv), 2-chloropyridine (1.2 equiv), KOH (3.0 equiv), and 18-crown-6 (0.05 equiv) in toluene (2.0 mL/mmol of **7**) was heated at reflux for 1 h with azeotropic removal of water. The reaction mixture was then cooled to room temperature and partitioned between ethyl acetate and water. The organics were washed (brine), dried ($MgSO_4$), filtered, concentrated in vacuo, and purified over silica gel to provide **8**.

Halobenzyloxypyridinium Triflates 1 (General Procedure)

Methyl triflate (1.1 equiv) was added to an ice-cold solution of pyridine **8** (1.0 equiv) in toluene (1.0 mL/mmol of **8**) under argon. The ice bath was removed, and a precipitate formed. The slurry was diluted with hexanes and filtered to collect the precipitate, which was dried under vacuum overnight to yield triflate salts **1** as white crystalline solids.

Halobenzyl Ethers 3 (General Procedure)

A mixture of alcohol **2** (1.0 equiv), OPT salt **1** (2.0 equiv), and MgO (2.0 equiv) in trifluorotoluene (2.0 mL/mmol of **2**) was heated in an oil bath at

100°C for 24 h. The reaction mixture was filtered through Celite®, the filtrate was concentrated in vacuo, and the resulting residue was purified over silica gel to provide **3**.

2-(4-Bromo-benzyloxy)-pyridine (8a)

Colorless oil (1.370 g, 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (dd, $J = 5.1$, 1.4, 1H), 7.59 (ddd, $J = 8.3$, 7.2, 2.0 Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H), 6.89 (ddd, $J = 7.1$, 5.1, 0.8 Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 146.8, 138.7, 136.5, 131.5, 129.5, 121.7, 117.0, 111.2, 66.6.

2-(4-Chloro-benzyloxy)-pyridine (8b)

Colorless oil (683 mg, 96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, $J = 5.1$, 1.9 Hz, 1H), 7.63–7.57 (m, 1H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.5$ Hz, 2H), 6.92–6.88 (m, 1H), 6.81 (dd, $J = 8.3$, 0.7 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 146.8, 138.6, 135.9, 133.5, 129.2, 128.5, 117.0, 111.2, 66.5.

2-(4-Iodo-benzyloxy)-pyridine (8c)

Colorless oil (1.056 g, 99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (dd, $J = 5.1$, 1.4 Hz, 1H), 7.69 (d, $J = 8.3$ Hz, 2H), 7.59 (ddd, $J = 8.6$, 7.2, 2.0 Hz, 1H), 7.21 (d, $J = 8.3$ Hz, 2H), 6.89 (ddd, $J = 5.8$, 5.1, 0.7 Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 146.8, 138.6, 137.5, 137.2, 129.7, 117.0, 111.2, 93.2, 66.7.

2-(2-Bromo-benzyloxy)-pyridine (8d)

Colorless oil (665 mg, 95%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, $J = 4.9$ Hz, 1H), 7.63–7.53 (m, 3H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.17 (t, $J = 7.6$ Hz, 1H), 6.90 (t, $J = 6.1$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 5.48 (S, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 146.9, 138.6, 136.8, 132.6, 129.1, 127.3, 123.0, 117.0, 111.1, 67.0.

2-(4-Bromo-benzyloxy)-1-methylpyridinium Triflate (1a)

Colorless solid (1.856 g, 96%); mp: 119–121°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41–8.32 (m, 2H), 7.62–7.58 (m, 3H), 7.48–7.41 (m, 3H), 5.54 (s, 2H),

4.11 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 161.8, 150.0, 145.9, 135.0, 133.7, 132.4, 124.6, 120.8, 114.0, 75.0, 43.5; HRMS (ESI +) 278.0175 (M-OTf)$^+$ (calculated for $C_{13}H_{13}NOBr^+$ 278.0181).

2-(4-Chloro-benzyloxy)-1-methylpyridinium Triflate (1b)

Yield 726 mg (95%); mp: 116–118°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40–8.32 (m, 2H), 7.60 (d, J = 8.9 Hz, 1H), 7.51–7.42 (m, 5H), 5.56 (s, 2H), 4.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 145.9, 136.5, 134.6, 132.2, 130.8, 120.8, 114.0, 75.0, 43.6; HRMS (ESI +) 234.0670 (M-OTf)$^+$ (calculated for $C_{13}H_{13}NOCl^+$ 234.0680).

2-(4-Iodo-benzyloxy)-1-methylpyridinium Triflate (1c)

White crystalline solid. (91 mg, 96%); mp: 109–112°C ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, J = 6.3 Hz, 1H), 8.31 (t, J = 8.3 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.7 Hz, 1H), 7.40 (t, J = 6.5 Hz, 1H), 7.22 (d, J = 8.3 Hz, 2H), 5.44 (s, 2H), 4.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 147.8, 143.4, 137.8, 132.0, 130.0, 118.8, 116.3, 111.8, 95.1, 73.4, 41.7; HRMS (ESI +) 326.0030 (M-OTf)$^+$ (calculated for $C_{13}H_{13}NOI^+$ 326.0041).

2-(2-Bromo-benzyloxy)-1-methylpyridinium Triflate (1d)

White crystalline solid. (331.5 mg, 93%); mp: 98–100°C ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 5.8 Hz, 1H), 8.42 (t, J = 7.8 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 7.7 Hz, 2H), 7.47 (t, J = 6.7 Hz, 1H), 7.40 (t, J = 7.4 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 5.63 (s, 2H), 4.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 148.3, 144.1, 133.2, 131.9, 131.7, 128.2, 124.1, 119.3, 112.0, 74.0, 42.0; HRMS (ESI +) 278.0169 (M-OTf)$^+$ (calculated for $C_{13}H_{13}NOBr^+$ 278.0181).

1-(4-Bromo-benyzloxy)-4-(4-methoxyphenyl)-butane (3aa)

Colorless oil (91.3 mg, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.47 (t, J = 5.8 Hz, 2H), 2.58 (t, J = 7.0 Hz, 2H) 1.70–1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 137.7, 134.4, 131.4, 129.3, 129.2, 121.3, 113.7, 72.1, 70.1, 55.2, 34.8, 29.3, 28.2.

1-(4-Bromo-benyzloxy)-2-methyl-propionic Acid Methyl Ester (3ba)

Colorless oil (51.4 mg, 79%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8.3 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 4.46 (s, 2H), 3.69 (s, 3H), 3.64 (dd, J = 9.0, 7.4 Hz, 1H), 3.48 (dd, J = 9.0, 5.8 Hz, 1H), 2.78 (d of apparent quintets, J = 5.8, 7.2 Hz, 1H), 1.18 (d, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 137.2, 131.5, 129.2, 121.4, 72.3, 72.1, 51.7, 40.2, 14.0.

5α-Cholester-3ß-yl *p*-Bromobenzyl Ether (3ca)

White solid (125.3 mg, 92%); mp: 128–132°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 5.27 (d, J = 4.8 Hz, 1H), 4.43 (s, 2H), 3.18 (m, 1H), 2.36–2.16 (m, 2H), 1.97–0.83 (m, 26H), 0.94 (s, 3H), 0.84 (d, J = 6.5 Hz, 3H), 0.792 (d, J = 6.6 Hz, 6H), 0.60 9s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 138.2, 131.4, 129.1, 121.7, 121.2, 78.8, 69.1, 56.8, 56.2, 50.2, 42.3, 39.8, 39.5, 39.2, 37.2, 36.9, 36.2, 35.8, 32.0, 31.9, 28.4, 28.2, 28.0, 24.3, 23.9, 22.8, 22.6, 21.1, 19.4, 18.7, 11.9.

1-(4-Bromo-benyzloxy)-adamantane (3ea)

White solid (53.1 mg, 86%); mp: 48–49°C ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 4.37 (s, 2H), 2.09 (br s, 3H), 1.74 (br s, 6H), 1.56 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 131.3, 129.0, 120.8, 72.9, 61.6, 41.7, 36.5, 30.6.

5α-Cholester-3ß-yl *p*-Chlorobenzyl Ether (3cb)

White solid (95 mg, 93%); mp: 136–139°C ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.19 (m, 4H), 5.27 (d, J = 5.1 Hz, 1H), 4.45 (s, 2H), 3.18 (tt, J = 11.1, 4.4, 1H), 2.33 (ddd, J = 13.1, 4.6, 1.9, 1H), 2.24–2.15 (m, 1H), (m, 26H), 0.94 (s, 3H), 0.84 (d, J = 6.5 Hz, 3H), 0.79 (d, J = 6.6 Hz, 6H), 0.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 137.6, 133.1, 128.8, 128.4, 121.7, 78.8, 69.1, 56.8, 56.2, 50.2, 42.3, 39.8, 39.5, 39.1, 37.2, 36.9, 36.2, 35.8, 32.0, 31.9, 28.4, 28.2, 28.0, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.7, 11.9.

1-(2-Bromo-benyzloxy)-1-phenylpropane (3dd)

Yield 72 mg (95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.45 (m, 2H), 7.31–7.09 (m, 7H), 4.54 (s, 2H), 3.55 (t, J = 6.3 Hz, 2H), 2.73 (d, J = 8.0 Hz, 2H),

1.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 142.3, 136.8, 133.4, 133.1, 132.8, 132.7, 131.7 130.1, 127.0, 76.5, 74.4, 36.7, 35.7.

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