A Highly Efficient and Convenient Method for the Direct Conversion of Alkyl THP Ethers into the Corresponding Alkyl Benzyl Ethers

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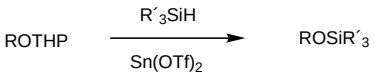
Abstract: Direct conversion of alcohol tetrahydropyranyl (THP) ethers into the corresponding benzyl ethers can be conveniently performed by reaction with triethylsilane and benzaldehyde in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in a one-pot procedure.

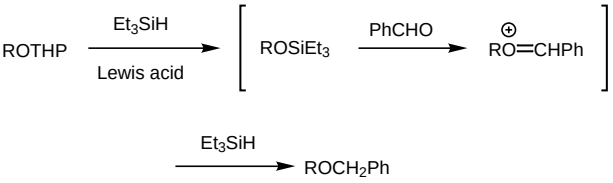
Key words: THP ethers, benzyl ethers, triethylsilane, benzaldehyde, one-step conversion of protecting group

Alkyl ethers such as benzyl and substituted benzyl ethers are important functional groups in synthetic organic chemistry and have been widely used as protecting groups of the hydroxyl function as well as other-type protecting groups such as silyl ether, acetal and ester types.[1] Dialkyl ethers are generally formed by the treatment of parent alcohols with the corresponding alkyl halides under the influence of a base such as sodium hydride,[2] sodium hydroxide,[3] and so on. Direct transformation between the four typical types of protecting groups of the hydroxyl function is of great importance from the standpoint of efficiency (time, reagent) and convenience.

In our series of studies[4] on the direct transformation of a protecting group of the hydroxyl function into another, we have previously demonstrated that direct conversion of aryl trialkylsilyl ethers and aryl acetates into the corresponding aryl benzyl ethers can be conveniently performed by reaction with benzyl bromide under the influence of cesium fluoride and sodium methoxide, respectively.[5] However, direct conversion of alcohol tetrahydropyranyl (THP) ethers into the corresponding benzyl ethers has not been reported. On the other hand, we had found that alcohol THP ethers can be readily converted into silyl ether-protected alcohols in good yields by reaction with trialkylsilane in the presence of tin(II) trifluoromethanesulfonate ($Sn(OTf)_2$) (Scheme 1).[4e] This result suggested that the reaction of alcohol THP ethers with benzaldehyde and triethylsilane under the influence of a Lewis acid catalyst would afford directly the corresponding benzyl ethers via reduction of the oxonium ions[6] (Scheme 2). In this communication, we wish to report a highly efficient and convenient method for the direct conversion of alkyl THP ethers into the corresponding alkyl benzyl ethers in a one-pot procedure.

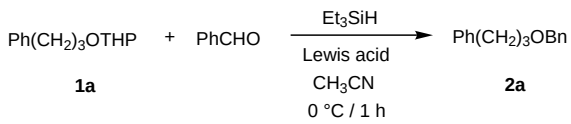


Scheme 1



Scheme 2

First, we examined the reaction of the THP ether of 3-phenylpropanol (**1a**) with triethylsilane (2.2 equiv) and benzaldehyde (1.1 equiv) under the influence of 0.1 equivalent of $Sn(OTf)_2$ in acetonitrile (Scheme 3).After 1 h at 0°C, the usual workup of the reaction mixture gave the desired benzyl ether of 3-phenylpropanol (**2a**) in 96% yield (Table 1, Run 1). In a screening of other Lewis acid catalysts, we found that using 0.1 equivalent of trimethylsilyl triflate (TMSOTf) afforded the best result (Table 1, Run 4). However, when the amount of TMSOTf was reduced to 0.03 equivalent, the yield of benzyl ether was slightly decreased (Table 1, Run 5). We have, therefore, tentatively chosen a combination of the THP ether, triethylsilane, benzaldehyde, and TMSOTf (molar ratio; 1:2.2:1.1:0.1) as the optimum reaction condition.



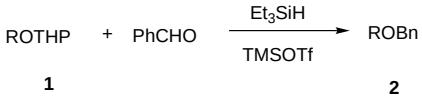
Scheme 3

Table 1 The Effect of Lewis Acid in the Conversion of THP Ether **1a** to Benzyl Ether **2a**[a]

Run	Lewis Acid (equiv)	Yield of **2a** (%)[b]
1	$Sn(OTf)_2$ (0.1)	96
2	$BF_3{\cdot}OEt_2$ (0.1)	20
3	TMSI (0.1)	88
4	TMSOTf (0.1)	98
5	TMSOTf (0.03)	90

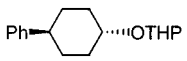
[a] Molar ratio of THP ether/Et_3SiH/PhCHO = 1:2.2:1.1.
[b] Isolated yield of purified product.

Representative examples of direct conversion of alcohol THP ethers into the corresponding benzyl ethers are given in Table 2. As can be seen, the reaction was successful with the THP ethers of secondary alcohols (**1b** and **1c**) as well as primary alcohols (Runs 2 and 3). In the presence of other-type protecting groups, such as benzyl ether (**1d**) and benzoate (**1e**), THP ethers are selectively transformed into the corresponding benzyl ethers in excellent yields (Runs 4 and 5). It is worth pointing out that an aromatic ketone (**1f**), which is reducible by triethylsilane under acidic conditions,[7] is tolerated under these reaction conditions (Run 6). However, the reaction of aryl THP ethers resulted in deprotection of THP group to yield the corresponding phenols.



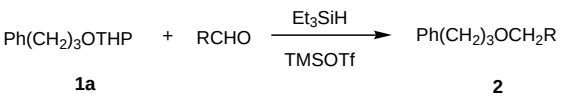
Scheme 4

Table 2 Synthesis of Various Benzyl Ethers from THP Ethers[a]

Run	ROTHP		Product	Yield of **2**[b] (%)
1	$Ph(CH_2)_2CH_2OTHP$	**1a**	**2a**	98
2	$Ph(CH_2)_2CH(Me)OTHP$	**1b**	**2b**	95
3		**1c**	**2c**	97
4	$BnO(CH_2)_3CH_2OTHP$	**1d**	**2d**	95
5	$PhCO_2(CH_2)_3CH_2OTHP$	**1e**	**2e**	98
6	$4\text{-}MeCOC_6H_4(CH_2)_2CH_2OTHP$	**1f**	**2f**	90

[a] Reaction was carried out at 0 °C for 1 h in MeCN. Molar ratio of THP ether/ Et_3SiH/PhCHO/TMSOTf = 1:2.2:1.1:0.1.
[b] Isolated yield of purified product.

Next, we examined the direct conversion of THP ethers into various substituted benzyl ethers. As shown in Table 3, various *p*-substituted benzyl ethers are obtained in good yields with the use of the corresponding *p*-substituted benzaldehyde instead of benzaldehyde. *p*-Methoxybenzyl (PMB) ether (**2i**), which is frequently used as a protecting group as well as unsubstituted benzyl ether, is obtained from the reaction with *p*-methoxybenzaldehyde (Run 3). This method is a new access to the synthesis of various substituted benzyl ethers from protected alcohols, not from parent alcohols.



Scheme 5

Table 3 Synthesis of Various Substituted Benzyl Ethers from THP Ethers[a]

Run	RCHO	Product	Yield of **2**[b] (%)
1	$4\text{-}ClC_6H_4CHO$	**2g**	95
2	$4\text{-}NO_2C_6H_4CHO$	**2h**	90
3	$4\text{-}MeOC_6H_4CHO$	**2i**	90[c]
4	$4\text{-}MeC_6H_4CHO$	**2j**	98

[a] Unless otherwise mentioned, reaction was carried out at 0 °C for 1 h in MeCN. Molar ratio of THP ether/Et_3SiH/RCHO/TMSOTf = 1:2.2:1.1:0.1.
[b] Isolated yield of purified product.
[c] Reaction was carried out at –40 °C for 15 min. TMSOTf (0.05 equiv).

In summary, the present direct conversion of THP ethers into the benzyl ethers has the following synthetic advantages:1) high efficiency 2) mild reaction conditions 3) one-pot procedure 4) chemoselectivity toward THP ethers. In our series of studies on the one-step conversion between typical protecting groups of the hydroxyl function, we have added a new, direct conversion of THP ethers into benzyl ethers.

All reactions were carried out under argon atmosphere. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz on a JEOL GSX-400, respectively. The chemical shifts are reported in ppm (δ) relative to TMS in $CDCl_3$. IR spectra were recorded in cm^{-1} on a JASCO FT/IR-300E. MeCN was distilled from CaH_2. TLC was performed on Wakogel B-5F silica gel with Et_2O and hexane as eluents.

1-Benzyloxy-3-phenylpropane (2a); Typical Procedure
To a solution of **1a** (66.1 mg, 0.30 mmol) and Et_3SiH (76.7 mg, 0.66 mmol) in MeCN (1 mL) was added a solution TMSOTf (6.7 mg, 0.03 mmol) in MeCN (0.5 mL) and a solution of benzaldehyde (35.0 mg, 0.33 mmol) in MeCN (1.0 mL) sequentially at 0°C under an argon atmosphere. The mixture was stirred for 1 h at this temperature and quenched with satd aq $NaHCO_3$ solution. The organic materials were extracted with CH_2Cl_2 and dried (Na_2SO_4). The solvent was evaporated and the product **2a** (66.5 mg, 98%) was isolated by TLC on silica gel (Et_2O/hexane, 1:10).

^1H NMR: 1.94 (m, 2 H), 2.71 (t, 2 H, *J* = 8.0 Hz), 3.49 (t, 2 H, *J* = 6.4 Hz), 4.50 (s, 2 H), 7.17 (m, 3 H), 7.28 (m, 3 H), 7.35 (m, 4 H).

^{13}C NMR: 31.34, 32.33, 69.44, 72.86, 125.70, 127.49, 127.61, 128.26, 128.32, 128.44, 138.55, 141.94.

IR (neat): 730, 1100, 1460, 2860 cm^{-1}.

2-Benzyloxy-4-phenylbutane (2b)
^1H NMR: 1.23 (d, 3 H, *J* = 6.4 Hz), 1.76 (m, 1 H), 1.92 (m, 1 H), 2.62–2.80 (m, 2 H), 3.54 (m, 1 H), 4.45 (d, 1 H, *J* = 12.0 Hz), 4.58 (d, 1 H, *J* = 12.0 Hz), 7.17 (m, 3 H), 7.27 (m, 3 H), 7.35 (m, 4 H).

^{13}C NMR: 19.62, 31.83, 38.45, 70.34, 74.14, 125.67, 127.42, 127.68, 128.31, 128.34, 128.42, 139.03, 142.40.

IR (neat):735, 1065, 1454, 2927 cm^{-1}.

***trans*-1-Benzyloxy-4-phenylcyclohexane (2c)**
^1H NMR: 1.41–1.54 (m, 4 H), 1.95 (m, 2 H), 2.23 (m, 2 H), 2.51 (m, 1 H), 3.41 (m, 1 H), 4.60 (s, 2 H), 7.19 (m, 3 H), 7.26 (m, 3 H), 7.33 (m, 4 H).

^{13}C NMR: 2.49, 32.67, 43.72, 69.92, 77.32, 126.00, 126.74, 127.39, 127.53, 128.34, 139.09, 146.67.

IR (neat): 737, 1100, 1450, 2926 cm^{-1}.

1,4-Dibenzyloxybutane (2d)
^{1}H NMR: 1.71 (m, 4 H), 3.49 (m, 4 H), 4.50 (s, 4 H), 7.25 (m, 4 H), 7.33 (m, 6 H).

^{13}C NMR: 26.50, 70.12, 72.84, 127.47, 127.60, 128.34, 138.60.

IR (neat): 734, 1099, 1454, 2855 cm^{-1}.

1-Benzoyloxy-4-benzyloxybutane (2e)
^{1}H NMR: 1.79 (m, 2 H), 1.88 (m, 2 H), 3.54 (t, 2 H, *J* = 6.4 Hz), 4.85 (t, 2 H, *J* = 6.4 Hz), 4.52 (s, 2 H), 7.28 (m, 2 H), 7.34 (m, 3 H), 7.43 (m, 2 H), 7.55 (m, 1 H), 8.03 (m, 2 H).

^{13}C NMR: 25.63, 26.40, 64.79, 69.76, 72.94, 127.56, 127.61, 128.31, 128.37, 129.53, 130.39, 132.83, 138.44, 166.63.

IR (neat): 712, 1110, 1274, 1718 cm^{-1}.

1-(4-Acetylphenyl)-4-benzyloxypropane (2f)
^{1}H NMR: 1.94 (m, 2 H), 2.58 (s, 3 H), 2.78 (t, 2 H, *J* = 8.0 Hz), 3.48 (t, 2 H, *J* = 6.0 Hz), 4.51 (s, 2 H), 7.26 (d, 2 H, *J* = 8.0 Hz), 7.31 (m, 2 H), 7.34 (m, 3 H), 7.87 (d, 2 H, *J* = 8.0 Hz).

^{13}C NMR: 26.54, 31.00, 32.41, 69.16, 72.97, 127.60, 127.68, 128.39, 128.51, 128.69, 135.04, 138.41, 147.88, 197.88.

IR (neat): 737, 1102, 1267, 1358, 1606, 1681, 2857 cm^{-1}.

1-(4-Chlorobenzyloxy)-3-phenylpropane (2g)
^{1}H NMR: 1.93 (m, 2 H), 2.71 (t, 2 H, *J* = 7.6 Hz), 3.47 (t, 2 H, *J* = 6.4 Hz), 4.61 (s, 2 H), 7.18 (m, 3 H), 7.28 (m, 6 H).

^{13}C NMR: 31.27, 32.33, 69.58, 72.10, 125.80, 128.32, 128.45, 128.50, 128.94, 133.24, 137.05, 141.84.

IR (neat): 700, 1088, 1491, 2858 cm^{-1}.

1-(4-Nitrobenzyloxy)-3-phenylpropane (2h)
^{1}H NMR: 1.98 (m, 2 H), 2.74 (t, 2 H, *J* = 7.6 Hz), 3.54 (t, 2 H, *J* = 6.0 Hz), 4.59 (s, 2 H), 7.18 (m, 3 H), 7.28 (m, 2 H), 7.50 (d, 2 H, *J* = 8.8 Hz), 8.21 (d, 2 H, *J* = 8.8 Hz).

^{13}C NMR: 21.01, 29.71, 38.51, 48.08, 55.24, 77.32, 101.35, 113.79, 129.08, 134.08, 134.09, 157.75.

IR (neat): 738, 1105, 1346, 1419 cm^{-1}.

1-(4-Methoxybenzyloxy)-3-phenylpropane (2i)
^{1}H NMR: 1.92 (m, 2 H), 2.70 (t, 2 H, *J* = 8.4 Hz), 3.46 (t, 2 H, *J* = 6.0 Hz), 3.81 (s, 3 H), 4.43 (s, 2 H), 6.88 (d, 2 H, *J* = 8.8 Hz), 7.18 (m, 3 H), 7.26 (m, 4 H).

^{13}C NMR: 31.35, 32.38, 55.26, 69.19, 72.56, 113.75, 125.71, 128.28, 128.47, 129.26, 130.65, 142.00, 159.12.

IR (neat): 700, 1035, 1099, 1247, 1512, 2935 cm^{-1}.

1-(4-Methylbenzyloxy)-3-phenylpropane (2j)
^{1}H NMR: 1.92 (m, 2 H), 2.35 (s, 3 H), 2.71 (t, 2 H, *J* = 8.0 Hz), 3.47 (t, 2 H, *J* = 6.4 Hz), 4.46 (s, 2 H), 7.16 (m, 5 H), 7.26 (m, 4 H).

^{13}C NMR: 21.15, 31.37, 32.36, 69.30, 72.76, 125.70, 127.79, 128.28, 128.47, 129.02, 135.49, 137.19, 142.02.

IR (neat): 746, 802, 1101, 1454, 2856 cm^{-1}.

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