A Novel and Chemoselective Transformation of Alcohol Silyl Ethers into the Corresponding Tetrahydropyranyl Ethers

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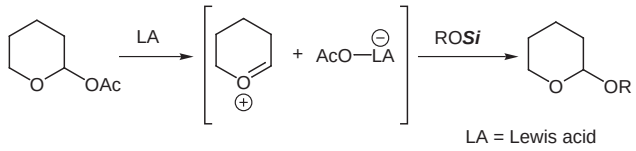
Abstract: Direct conversion of alcohol silyl ethers into the corresponding tetrahydropyranyl (THP) ethers can be easily performed by reaction with THP acetate under the influence of a catalytic amount of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf). Aliphatic TBS ether can be selectively transformed into the corresponding THP ether in the presence of phenolic TBS ether.

Key words: silyl ether, THP ether, THP acetate, *tert*-butyldimethylsilyl trifluoromethanesulfonate, one-step conversion of protective group, chemoselectivity

Protective groups of hydroxy functions are indispensable in synthetic organic chemistry, and various types of protective groups, such as alkyl ether, silyl ether, acetal, and ester types are utilized for the protection of hydroxy functions.[1] These protective groups are complementary to each other, and an appropriate protective group has to be chosen carefully according to the intended reaction conditions. The transformation of one protective group into another involving deprotection and protection-anew is frequently required. Therefore, one-pot transformation between the typical protecting groups of the hydroxyl function is of great importance from the standpoint of efficiency (time, reagent) and convenience.[2] In recent years, several efficient methods for this purpose have been developed in our laboratory.[3]

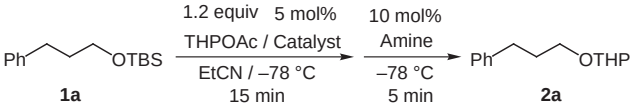
Alcohol silyl ethers, as versatile protective groups of hydroxy functions, have played an important role in synthetic organic chemistry and various types of silyl ethers have been reported so far.[1,4] On the other hand, tetrahydropyranyl (THP) ether is widely used as a traditional acetal-type protective group of the hydroxy function, and it is generally formed by the treatment of parent alcohols with dihydropyran under the influence of an acid catalyst.[5] Much more recently, we found that silyl ethers were smoothly converted into the corresponding diphenylmethyl (DPM) ethers by reaction with diphenylmethyl formate (HCO_2DPM), catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf).[6] In this reaction, the diphenylmethyl cation generated from HCO_2DPM under Lewis acid conditions was presumed to be an active species, and it reacted readily with alkyl silyl ether to provide the corresponding alkyl DPM ether. This promising result suggested that alkyl THP ethers could be obtained from the corresponding alkyl silyl ethers (not from the parent alcohols) by reaction with the oxonium cation generated from THP acetate (THPOAc) under the influence of a Lewis acid catalyst (Scheme 1).



Scheme 1

In this communication, we wish to report a highly efficient and convenient method for the direct conversion of alkyl trialkylsilyl ethers into the corresponding THP ethers. In the first place, we examined the reaction of the TBS ether of 3-phenylpropanol (**1a**) and THPOAc in the presence of 5 mol% of TMSOTf. After the usual workup, the desired THP ether **2a** was obtained in 87% yield (Table 1, run 1). After screening various reaction conditions, we found that the addition of 10 mol% of triethylamine after stirring the mixture of TBS ether, THPOAc, and TMSOTf, improved the yield of the THP ether (Table 1, run 2). Furthermore, the use of TBSOTf in place of TMSOTf gave the better result (Table 1, run 3). By using a stoichiometric amount of $BF_3{\bullet}OEt_2$, the corresponding TBS ether was obtained in moderate yield (Table 1, run 7).

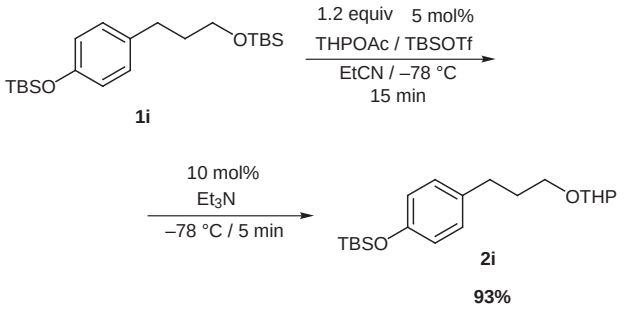
Table 1 Synthesis of 3-Phenylpropanol THP Ether from TBS Ether



Run	Catalyst	Amine	Yield of **2a** (%)[a]
1[b]	TMSOTf	–	87
2	TMSOTf	Et_3N	93
3	TBSOTf	Et_3N	96
4	TBSOTf	*i*-Pr_2NEt	95
5	TfOH	Et_3N	90
6	$BF_3{\cdot}OEt_2$	Et_3N	trace
7[b, c]	$BF_3{\cdot}OEt_2$	–	71

[a] Isolated yield of chromatographically purified product.
[b] Reaction was performed for 20 min.
[c] 100 mol% of $BF_3{\cdot}OEt_2$ was used.

Representative examples of this direct conversion of various alcohol TBS ethers into the corresponding THP ethers are collected in Table 2. TBS ethers of primary and secondary alcohols **1a–c** were transformed into the corresponding THP ethers **2a–c**, respectively, in high yields (Table 2, runs 1–3). However, in the case of the TBS ether of a sterically hindered tertiary alcohol **1d**, no formation of the desired THP ether was observed (Table 2, run 4). In the case of substrates having other functional groups such as benzyl (Bn) ether **1e**, benzoate **1f**, and THP ether **1g**, the TBS ether moieties were transformed with high selectivity into the corresponding THP ethers **2e**, **2f** and **2g** (Table 2, runs 5–7). Contrary to that, direct conversion of the TBS ether of *p*-cresol (**1h**) into the THP ether was not operative at all under the same reaction conditions (Table 2, run 8). This result suggested that chemoselective transformation of aliphatic TBS ether in the presence of phenolic TBS ether could be readily performed. Scheme 2 shows the reaction starting from the TBS ether of 3-(4-hydroxyphenyl)propanol (**1i**). Aliphatic TBS ether was selectively converted into the THP ether while phenolic TBS ether was inert. The corresponding mono-THP ether bearing a phenolic TBS ether moiety (**2i**) was successfully obtained in 93% yield.

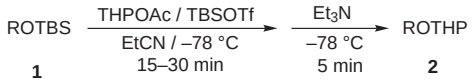


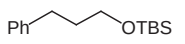
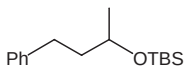
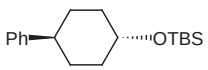
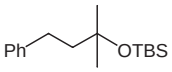
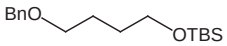
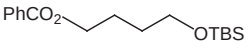
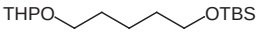
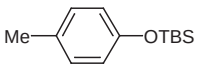
Scheme 2

Next, we examined the scope of trialkylsilyl ethers. The reaction was conducted with various silyl ethers of 3-phenylpropanol (Table 3). Triethylsilyl (TES) ether **1j** and triisopropylsilyl (TIPS) ether **1k** could also be converted into the corresponding THP ethers in high yields (Table 3, runs 1 and 2). However, in the case of sterically bulky *tert*-butyldiphenylsilyl (TBDPS) ether **1l**, the reaction was very sluggish and the THP ether was scarcely obtained (Table 3, run 3). As it can be seen from Table 3, it is strongly indicated that the TBS ether could be selectively transformed into the THP ether in the presence of the TBDPS ether. Finally, we investigated the subtle chemoselectivity between the TBS and TBDPS ethers. The TBS ether was selectively transformed into the THP ether, and the corresponding mono THP ether **2m** was successfully obtained in 93% yield as depicted in Scheme 3.

In summary, the present direct conversion of alcohol silyl ethers into THP ethers has the following synthetic advantages: 1) high efficiency, 2) simple operation, 3), one-pot procedure and 4) high chemoselectivity. In our series of investigation on the one-step conversion between typical protecting groups of the hydroxy function, we have added a new direct transformation of silyl ethers into THP ethers.

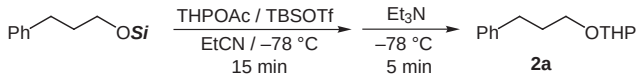
Table 2 Synthesis of Various THP Ethers from TBS Ethers



Run[a]	ROTBS		Product	Yield of **2** (%)[b]
1		**(1a)**	**2a**	96
2		**(1b)**	**2b**	88
3		**(1c)**	**2c**	90
4		**(1d)**	**2d**	0[c]
5		**(1e)**	**2e**	93
6		**(1f)**	**2f**	90
7		**(1g)**	**2g**	95
8		**(1h)**	**2h**	0[d]

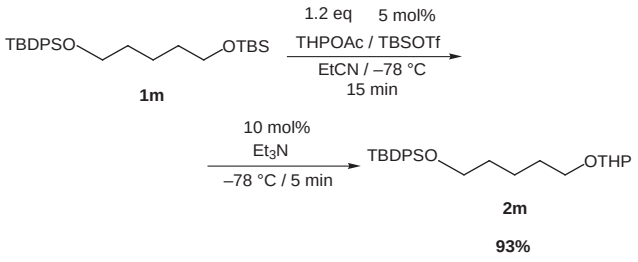
[a] Molar ratio of TBS ether : THPOAc : TBSOTf : Et_3N = 1 : 1.2 : 0.05 : 0.1.
[b] Isolated yield of chromatographically purified product.
[c] 81% of TBS ether was recovered.
[d] 94% of TBS ether was recovered.

Table 3 Synthesis of THP Ether from Various Silyl Ethers



Run[a]	*Si*		Yield of **2a** (%)[b]
1	TES	**(1j)**	90
2	TIPS	**(1k)**	94
3	TBDPS	**(1l)**	trace[c]

[a] Molar ratio of silyl ether:THPOAc:TBSOTf:Et_3N = 1:1.2:0.05:0.1.
[b] Isolated yield of chromatographically purified product.
[c] 89% of TBDPS ether was recovered.



Scheme 3

All reactions were carried out under argon atmosphere. ^{1}H 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. EtCN was distilled from CaH_2. TLC were performed on Wakogel B-5F silica gel with Et_2O and hexane as eluents.

2-(3-Phenylpropyloxy)tetrahydropyran (2a); Typical Procedure

To a solution of *tert*-butyldimethyl-(3-phenylpropyloxy)silane (75.1 mg, 0.300 mmol) and THPOAc (51.9 mg, 0.360 mmol) in EtCN (1.6 mL) was added a solution of TBSOTf (3.5 μL, 0.015 mmol) in EtCN (0.4 mL) at −78 °C under argon. After stirring for 15 min, a solution of Et_3N (3.0 mg) in EtCN (0.4 mL) was added. The reaction mixture was stirred for 5 min at −78 °C and quenched with phosphate buffer (pH 7). The organic materials were extracted with Et_2O and dried ($MgSO_4$). The solvent was evaporated and the product **2a** (63.4 mg, 96%) was isolated by TLC on silica gel (Et_2O/hexane, 1:7).

^{1}H NMR: δ = 1.58 (m, 4 H), 1.72 (m, 1 H), 1.85 (m, 1 H), 1.93 (m, 2 H), 2.71 (m, 2 H), 3.41 (m, 1 H), 3.49 (m, 1 H), 3.77 (m, 1 H), 3.88 (m, 1 H), 4.58 (m, 1 H), 7.13 (m, 3 H), 7.27 (m, 2 H).

^{13}C NMR: δ = 19.67, 25.49, 30.77, 31.34, 32.48, 62.36, 66.87, 98.92, 125.72, 128.29, 128.44, 142.05.

IR (neat): ν = 700, 745, 1033, 1077, 1353, 1454, 2942 cm^{-1}.

2-(1-Methyl-3-phenylpropoxy)tetrahydropyran (2b)

^{1}H NMR: δ = 1.16 (d, 1.5 H, *J* = 6.4 Hz), 1.28 (d, 1.5 H, *J* = 6.4 Hz), 1.57 (m, 4 H), 1.86 (m, 4 H), 2.76 (m, 2 H), 3.49 (m, 1 H), 3.84 (m, 2 H), 4.63 (m, 0.5 H), 4.73 (m, 0.5 H), 7.27 (m, 5 H).

^{13}C NMR: δ = 19.81, 21.64, 25.50, 31.27, 32.21, 39.24, 62.88, 73.66, 98.96, 125.72, 128.31, 128.39, 142.57.

IR (neat): ν = 699, 1023, 1132, 1375, 1453, 2940 cm^{-1}.

***trans*-2-(4-Phenylcyclohexyloxy)tetrahydropyran (2c)**

^{1}H NMR: δ = 1.46 (m, 8 H), 1.74 (m, 1 H), 1.91 (m, 3 H), 2.15 (m, 2 H), 2.50 (m, 1 H), 3.51 (m, 1 H), 3.68 (m, 1 H), 3.96 (m, 1 H), 4.76 (m, 1 H), 7.18 (m, 3 H), 7.27 (m, 2 H).

^{13}C NMR: δ = 20.00, 25.50, 31.16, 31.26, 32.46, 32.71, 33.96, 43.62, 62.82, 74.68, 96.81, 125.98, 126.76, 128.32, 164.75.

IR (KBr): ν = 699, 758, 1024, 1116, 1350, 1449, 2928 cm^{-1}.

2-(4-Benzyloxybutoxy)tetrahydropyran (2e)

^{1}H NMR: δ = 1.54 (m, 4 H), 1.72 (m, 5 H), 1.81 (m, 1 H), 3.41 (m, 1 H), 3.50 (m, 3 H), 3.76 (m, 1 H), 3.85 (m, 1 H), 4.51 (s, 2 H), 4.57 (m, 1 H), 7.30 (m, 5 H).

^{13}C NMR: δ = 19.59, 25.49, 26.50, 26.62, 30.74, 62.23, 67.28, 70.20, 72.87, 98.77, 127.47, 127.60, 128.32, 138.65.

IR (neat): ν = 698, 735, 1033, 1120, 1200, 1363, 1454, 2940 cm^{-1}.

4-(Tetrahydropyran-2-yloxy)butyl Benzoate (2f)

^{1}H NMR: δ = 1.58 (m, 3 H), 1.80 (m, 7 H), 3.49 (m, 2 H), 3.84 (m, 2 H), 4.36 (t, 2 H, *J* = 6.4 Hz), 4.59 (m, 1 H), 7.44 (t, 2 H, *J* = 7.8 Hz), 7.55 (t, 1 H, *J* = 7.6 Hz), 8.04 (d, 2 H, *J* = 6.8 Hz).

^{13}C NMR: δ = 19.62, 25.44, 25.72, 26.37, 30.70, 62.36, 64.84, 66.96, 98.88, 128.29, 129.53, 130.41, 132.80, 166.62.

IR (neat): ν = 712, 1034, 1071, 1118, 1275, 1720, 2944 cm^{-1}.

1,4-Bis(tetrahydropyran-2-yloxy)pentane (2g)

^{1}H NMR: δ = 1.57 (m, 16 H), 1.82 (m, 2 H), 3.39 (m, 2 H), 3.51 (m, 2 H), 3.75 (m, 2 H), 3.86 (m, 2 H), 4.58 (m, 2 H).

^{13}C NMR: δ = 19.65, 22.94, 25.50, 29.58, 30.77, 62.29, 67.48, 98.82.

IR (neat): ν = 1033, 1078, 1122, 1940 cm^{-1}.

***tert*-Butyldimethyl-4-[3-(tetrahydropyran-2-yloxy)propyl]phenoxysilane (2i)**

^{1}H NMR: δ = 0.18 (s, 6 H), 0.98 (s, 9 H), 1.56 (m, 4 H), 1.72 (m, 1 H), 1.86 (m, 3 H), 2.63 (m, 1 H), 3.39 (m, 1 H), 3.48 (m, 1 H), 3.75 (m, 1 H), 3.87 (m, 1 H), 4.57 (m, 1 H), 6.74 (d, 2 H, *J* = 8.4 Hz), 7.04 (d, 2 H, *J* = 8.4 Hz).

^{13}C NMR: δ = −4.45, 18.81, 19.67, 25.50, 25.69, 30.78, 31.46, 31.61, 62.33, 66.85, 98.88, 119.80, 129.21, 134.67, 153.58.

IR (neat): ν = 839, 917, 1258, 1509, 2937 cm^{-1}.

***tert*-Butyldiphenyl-[5-(tetrahydropyran-2-yloxy)pentyloxy]silane (2m)**

^{1}H NMR: δ = 1.04 (s, 9 H), 1.51 (m, 10 H), 1.70 (m, 1 H), 1.82 (m, 1 H), 3.37 (m, 1 H), 3.49 (m, 1 H), 3.66 (t, 2 H, *J* = 6.4 Hz), 3.72 (m, 1 H), 4.57 (m, 1 H), 7.39 (m, 6 H), 7.67 (d, 4 H, *J* = 8.0 Hz).

^{13}C NMR: δ = 19.21, 19.60, 22.55, 25.52, 26.86, 29.50, 30.75, 32.40, 62.21, 63.84, 67.51, 98.76, 127.57, 129.48, 135.57.

IR (neat): ν = 702, 1034, 1112, 1428, 2938 cm^{-1}.

Acknowledgement

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