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A Novel and Efficient Method for the Synthesis of Tetrahydropyranyl Ethers Catalyzed by $Sc(OTf)_3$

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Reaction of alcohols with dihydropyran in the presence of a catalytic amount of $Sc(OTf)_3$ provides efficiently the corresponding tetrahydropyranyl ethers. After the reaction, the catalyst can be recovered quantitatively from the aqueous media and reused without loss of the activity.

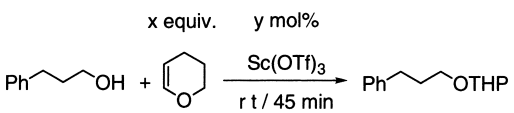
Tetrahydropyranyl (THP) ethers have been the most useful and representative protecting group of alcohols in synthetic organic chemistry.[1] THP ethers are very easy to introduce and to remove, as well as having general stability for most non-acidic reagents, so that several methods for the introduction of THP ether under various reaction conditions have been reported so far in the literature.[2] On the other hand, scandium(III) trifluoromethanesulfonate ($Sc(OTf)_3$) is a new type of water-soluble Lewis acid, and many useful reactions using $Sc(OTf)_3$ have been developed.[3] Our previous report has also documented that $Sc(OTf)_3$ is a very effective catalyst for the silylation of alcohols with methallylsilane.[4]

In this paper, we wish to report a useful and convenient procedure for the synthesis of THP ethers from the parent alcohols in the presence of a catalytic amount of $Sc(OTf)_3$.

In the first place, we examined the reaction of 3-phenyl-1-propanol as a model substrate with 3,4-dihydro-2*H*-pyran (DHP) in the presence of 5 mol% of $Sc(OTf)_3$ in dichloromethane. After 45 min, the usual work up of the reaction mixture gave the corresponding THP ether in 62% yield (Table 1, Run 1). In the case of using CH_3CN, the corresponding THP ether was obtained in lower yield (Table 1, Run 2). On the other hand, when ether solvents such as THF and DME were used, transformation took place very smoothly to give the THP ethers in high yields (Table 1, Runs 3–5). Furthermore, when the reaction was carried out with 1.8 equivalents of dihydropyran in the presence of 0.2 mol% of $Sc(OTf)_3$ in AcOEt for 1 h, the reaction proceeded very cleanly and the corresponding THP ether was obtained in 98% isolated yield without any other side products (Table 1, Run 7).

Representative and successful examples of syntheses of various alcohol THP ether are collected in Table 2.[5] Like primary

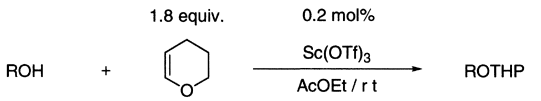
Table 1. The Effect of Various Reaction Conditions

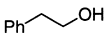
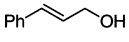
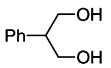
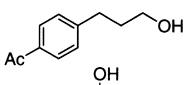
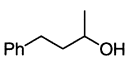
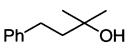
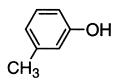
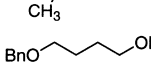
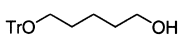
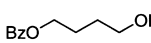
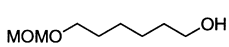
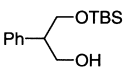
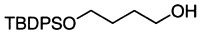


Run	*x*/equiv	*y*/mol%	Solvent	Yield[a]/%
1	1.2	5	CH_2Cl_2	62
2	1.2	5	CH_3CN	42
3	1.2	5	THF	91
4	1.2	5	DME	93
5[b]	1.5	0.2	DME	95
6[b]	1.5	0.2	AcOEt	96
7[b]	1.8	0.2	AcOEt	98

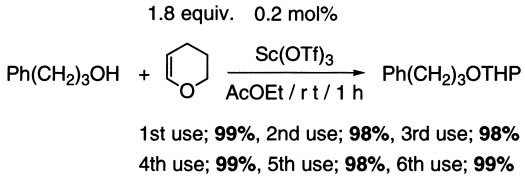
a) Isolated yields of purified product.
b) Reaction was carried out for 1 h.

Table 2. Synthesis of Various THP Ethers from Alcohols

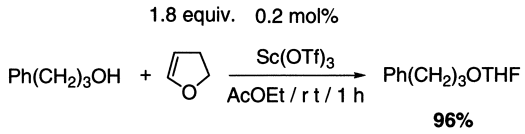


Run	ROH	Time/h	Yield[a]/%
1		1	95
2		1	97
3		1	98
4[b]		1	98
5		1	97
6		3	97
7		7	97
8		7	92
9[c]		24	86
10[c]		7	89
11		1	97
12		15	62
13		5	94
14		4	92
15		2	95
16		1	98

a) Isolated yields of purified product. b) 3 equiv of Dihydropyran were used. c) 0.05 mol% of $Sc(OTf)_3$ was used.



Scheme 1. Recovery and Reuse of $Sc(OTf)_3$.



Scheme 2. Synthesis of THF Ether.

alcohols, secondary alcohols, tertiary alcohol, and phenol were readily transformed into the corresponding THP ether in good to excellent yields. In the case of tertiary alcohol and phenol, the yields of THP ethers are slightly lower (Table 2, Runs 9 and 10). Additionally, alcohols having other functional groups underwent chemoselective reaction to give the THP ethers in excellent yields with no undesired reactions (Table 2, Runs 11–16). Especially, acid-sensitive functional groups such as an allylic alcohol, methoxymethyl ether, and *t*-butyldimethylsilyl ether were significantly unaffected under these reaction conditions (Table 2, Runs 3, 5, 14, and 15).

Next, we investigated the recovery and reuse of $Sc(OTf)_3$. After treatment of 3-phenyl-1-propanol with DHP under the optimal reaction conditions, the reaction mixture was quenched with water. Extraction with Et_2O afforded the desired THP ether in organic solvents. After the water was evaporated under reduced pressure, heating in vacuo at 200 °C for 2 h dried the resulting white powder. The catalyst was recovered quantitatively and reused at least six times without loss of the activity (Scheme 1).

Finally, we attempted the synthesis of tetrahydrofuranyl (THF) ether by the reaction of alcohol with 2,3-dihydrofuran instead of dihydropyran. The THF ether has also been used as an acetal-type protecting group for alcohols.[6] The corresponding THF ether was similarly obtained in 96% yield, as shown in Scheme 2.

In conclusion, we have developed a new method for the synthesis of tetrahydropyranyl ethers from alcohols catalyzed by $Sc(OTf)_3$. This method proceeded smoothly at room temperature under very mild reaction conditions. Additionally, the catalyst could be recovered quantitatively and reused without loss of the activity. These features show that this new method is very efficient and will be applicable to the synthesis of complex natural products.

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5 A typical experimental procedure is as follows (Table 1, Run 7): To a mixutre of scandium(Ⅲ) trifluoromethanesulfonate (1.0 mg, 0.0020 mmol) and 3-phenyl-1-propanol (136.2 mg, 1.0 mmol) in AcOEt (4 mL) was added 3,4-dihydro-2*H*-pyran (164 µL, 1.8 mmol) at room temperature under an argon atomsphere. The resultant mixture was stirred for 1 h at room temparature and quenched saturated sodium hydrogencarbonate. The organic materials were extracted with Et_2O and dried over anhydrous magnesium sulfate. The solvent was evaporated and 1-tetrahydropyranyloxy-3-phenylpropane (215.9 mg, 98%) was isolated by thin-layer chromatography on silica gel (ether:hexane = 1:3). The product gave satisfactory ^1H NMR and IR spectra.

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