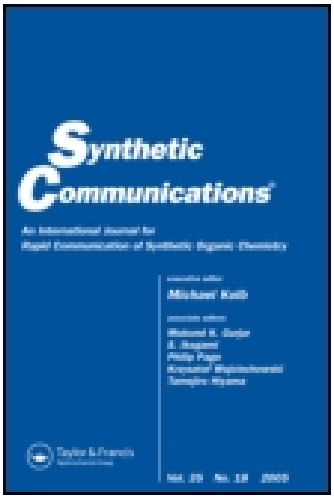

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Efficient and Ecofriendly Protocol for Tetrahydropyranylation/Depyranylation of Alcohols in the Presence of Tin(II) Chloride Dihydrate

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Abstract: A mild, efficient, and solvent-free protocol for tetrahydropyranylation of alcohols in the presence of a catalytic amount of $SnCl_2 \cdot 2H_2O$ is reported. Simple filtration of the reaction mixture through a short silica-gel pad gives the pure products in excellent yields. Depyranylation can also be achieved by adding methanol under similar reaction conditions.

Keywords: alcohols, microwave, solvent-free, tetrahydropyranylation

The protection of alcohols as tetrahydropyran[1] derivatives is one of the most sought after protocols in organic synthesis because of their easy introduction, greater stability toward hydrides, and alkylating reagents such as alkyl lithiums, Grignard reagents and so. Although $BF_3{\cdot}Et_2O$[2] is the most commonly used catalyst for tetrahydropyranylation of alcohols, its sensitivity toward moisture makes the synthetic chemists to look for better catalysts, as a result of which various catalysts such as $In(OTf)_3$,[3] p-TSA,[4] PPTS,[5] $ZrCl_4$,[6] I_2,[7] LiBr,[8] $InCl_3$ immobilized in ionic liquid,[9] acetonyltriphenyl phosphonium bromide (ATPB),[10] aluminium chloride hexahydrate,[11] TBATB,[12] $CuSO_4 \cdot 5H_2O$,[13] bromodimethyl sulphonium bromide,[14] dialkylimidazolium tetrachloroaluminates,[15] K-10 clay,[16] natural kaolinitic clay,[17] EPZG,[18] Y-zeolite,[19] alumina-supported zinc chloride,[20] and Nafion[21] were discovered to affect this transformation. Ironically, many of

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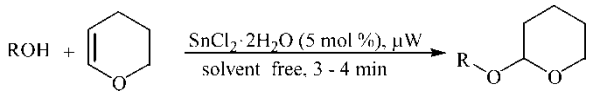
them suffer from difficulties such as longer reaction times, harsh reaction conditions, incompatibility with acid-sensitive functional groups,[2,9,11,12] removal of azeotropic mixture,[4,5] use of dehydrating reagents, involvement of expensive and moisture-sensitive catalysts,[3,4,10,14,15] and higher catalyst loading.[6,9,11,12,17,19–21]

Organic reactions under solvent-free conditions[22] have increasingly become popular because they are more environmentally favorable.[23] Moreover, recent years have witnessed phenomenal growth of microwave (MW) irradiation[24] in organic transformations.

In pursuance of our recent interest on microwave-accelerated reactions under solvent-free conditions,[25] we looked for a reagent system that would work under solvent-free conditions to make tetrahydropyranylation more environmentally favorable and clean, yet operationally simple and cost effective. We envisaged that tin(II) chloride, an extremely mild, cheap, easily available, and moisture-insensitive Lewis acid, might work as a wonderful catalytic system under solvent-free conditions to effect the transformation. In fact, when a ground mixture of *n*-octanol, 3,4-dihydro-2*H*-pyran (1 equiv) and 5 mol % of $SnCl_2 \cdot 2H_2O$ is irradiated with microwaves at 100 W for 4 min, complete tetrahydropyranylation takes place. In this communication, applications of our methodology (Scheme 1) using $SnCl_2 \cdot 2H_2O$ as an efficient catalyst for tetrahydropyranylation/depyranylation of various alcohols (Table 1) are reported.

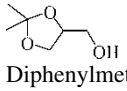
Various alcohols (Entries 1–20, Table 1) gave excellent yields of their corresponding THP ethers. Acid-sensitive functional groups such as acetoxy (Entries 11, 17), isopropylidene (Entry 15), OTBS (Entry 18), and reducible nitro group (Entry 3) are very much unaffected under this reaction condition as evident from their percentage of yields. Phenolic hydroxy groups (Entries 4, 14) remain unaffected under these conditions.[7] The allylic alcohols, cyclohex-2-en-1-ol and cinnamyl alcohol (Entry 19, 20), also generate their corresponding THP ethers in 93% and 91% yields respectively. It has been observed that *m*-hydroxybenzyl alcohol, 4-hydroxy-3-methoxy benzyl alcohol, gave only mono THP ethers, where phenolic hydroxy groups remained inert under this reaction condition. To study the inertness of phenols, when p-cresol (Entry 21) was treated with 3,4-dihydro-2*H*-pyran under similar reaction conditions, no THP ether formation was observed.

Interestingly, THP ether of benzyl alcohol undergoes cleavage upon microwave irradiation at 100 W within 3 min in the presence of the same catalyst (5 mol %) in methanol to give 89% yield (Scheme 2). It has been observed that THP ethers of other alcohols (Entries 1–10, Table 2) were



Scheme 1.

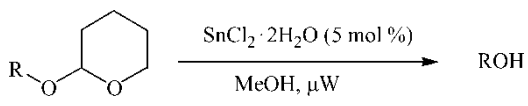
Table 1. Tetrahydropyranylation of alcohols via Scheme 1[a]

Entry	Substrates	Time (min)	Yield[b] (%)
1	$PhCH_2OH$	3	91
2	*p*-$ClC_6H_4CH_2OH$	3	95
3	*p*-$NO_2C_6H_4CH_2OH$	3	93
4	*m*-OH $C_6H_4CH_2OH$	3	88
5	*p*-$OMeC_6H_4CH_2OH$	3	92
6	*m*-$(CO_2Me)C_6H_4CH_2OH$	3	89
7	*n*-Octanol	4	87
8	Cyclohexanol	4	86
9	Menthol	4	90
10	Cholesterol	4	83
11	*m*-AcO $C_6H_4CH_2OH$	3	89
12	1-Phenyl ethanol	3	93
13	1-(p-Bromophenyl) ethanol	3	91
14	4-Hydroxy-3-methoxy benzyl alcohol	4	87
15		4	88
16	Diphenylmethanol	3	95
17	4-Aceoxy butan-1-ol	4	88
18	4-(t-Butyldimethylsilyloxoy) butan-1-ol	4	83
19	Cyclohex-2-en-1-ol	3	93
20	Cinnamyl alcohol	3	91
21	*o*-Cresol	10	—

[a]Microwave irradiation was done with a Samsung microwave, model 1630 N.
[b]Yield of the pure isolated product were characterized by ^1H NMR and IR spectroscopy.

also cleaved under similar reaction conditions to generate their corresponding alcohols in 80–91% yields.

In conclusion, we have established $SnCl_2 \cdot 2H_2O$ as an extremely effective catalyst for tetrahydropyranylation and depyranylation of alcohols containing acid labile and reducible functional groups such as acetoxy, nitro, OTBS, methoxy, carbomethoxy, and 1,3-dioxolane, which may find wide applicability in multistep synthesis. In contrast to some of the previously reported methods, our procedure is fast, is atom economic, and does not require an inert atmosphere, dehydrating agent, catalytic support, and aqueous workup. Simple filtration through a short silica-gel pad gave the pure products in very good yields.



Scheme 2.

Table 2. Depyranylation of THP ethers via Scheme 1

Entry	Products	Time (min)	Yield[a] (%)
1	$C_6H_4CH_2OH$	3	89
2	*n*-Octanol	3	81
3	*p*-$NO_2C_6H_4CH_2OH$	4	91
4	Cyclohexanol	4	82
5	*m*-AcO $C_6H_4CH_2OH$	3	82
6	1-(*p*-Bromophenyl) ethanol	3	86
7	4-Aceoxy butan-1-ol	4	81
8	4-(t-Butyldimethylsilyloxoy) butan-1-ol	4	80
9	Cyclohex-2-en-1-ol	3	82
10	Cinnamyl alcohol	3	87

[a]Yield of the pure isolated product was compared with starting alcohols and confirmed by ^{1}H NMR.

TYPICAL PROCEDURE

For tetrahydropyranylation, typically a mixture of *n*-octanol (0.260 g, 2 mmol), 3,4-dihydro-2*H*-pyran (0.168 g, 2 mmol), and $SnCl_2 \cdot 2H_2O$ (0.023 g, 0.1 mmol) was taken in an Erlen-Meyer flask and irradiated with microwaves at 100 W for 4 min. The reaction mixture was allowed to cool and filtered through a small silica-gel (60–120 mesh) pad with 1% ethyl acetate in hexane. Yield = 87% (0.372 g, 1.74 mmol). IR(KBr): 1040, 1075, 1128, 1360, 1469, 2860, 2921 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, $J = 6.5$ Hz, 3H), 1.25–1.35 (m, 10H), 1.42–1.77 (m, 8H), 3.35–3.41 (m, 1H), 3.45–3.50 (m, 1H), 3.63–3.71 (m, 1H), 3.79–3.86 (m, 1H), 4.57 (m, 1H).

For dehydropyranylation, a solution of THP ether of benzyl alcohol (0.384 g, 2 mmol) in methanol (2 mL) in a Erlen-Meyer flask was irradiated with microwaves with $SnCl_2 \cdot 2H_2O$ (0.023 g, 0.1 mmol) for 3 min, and the resulting solution was passed through a silica-gel column taking 10% ethyl acetate in hexane as eluent to obtain the desired benzyl alcohol in 89% (0.192 g, 1.78 mmol) yields.

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