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Facile Tetrahydropyranylation of Alcohols and Phenols Using Anhydrous Calcium Chloride under Mild and Neutral Conditions

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Summary. Treatment of 3,4-dihydro-2*H*-pyran with various alcohols and phenols in the presence of a catalytic amount of anhydrous calcium chloride in dichloromethane furnished tetrahydropyranyl ethers under almost neutral conditions.

Keywords. Tetrahydropyranylation; *THP* ethers; Alcohols and phenols; Anhydrous $CaCl_2$.

Introduction

The tetrahydropyranyl moiety (*THP*) is one of the most widely used protective groups employed in organic synthesis because of its low cost, the convenient preparation, its stability towards most non-acidic reagents, and the ease with which it can be removed. Although a number of methods are reported in the literature [1], some of these procedures suffer from using strongly acidic or expensive reagents. In addition to the well known protic and *Lewis* acids, other reagents and catalysts, such as iodotrimethylsilane [2], triphenylphosphine hydrobromide [3], montmorillonite clay [4], Envirocat EPZG [5], lithium perchlorate [6], and iodine [7] have been used to effect tetrahydropyranylation of alcohols. In spite of several efforts, the methods available for selective protection of alcohols as *THP* ethers and their deprotection without affecting acid and base sensitive functionalities present elsewhere in the molecule are limited [1]. Consequently, there is still a need to develop mild and efficient methods for tetrahydropyranylation of alcohols and phenols. We now report anhydrous calcium chloride as a mild and inexpensive catalyst for the tetrahydropyranylation of alcohols and phenols under neutral conditions (Scheme 1).

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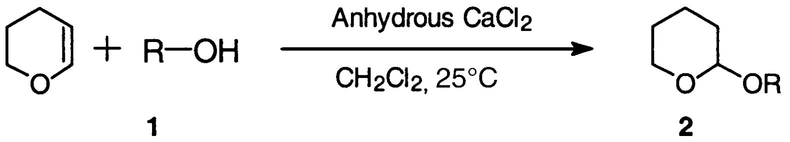
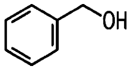
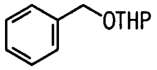
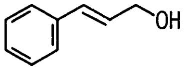
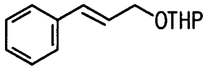
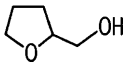
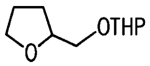
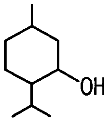
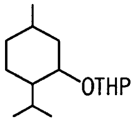
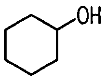
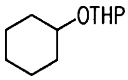
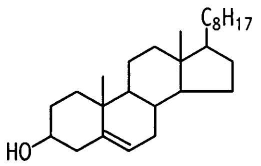
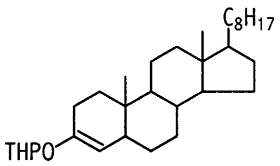


Scheme 1

Results and Discussion

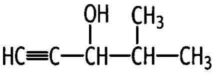
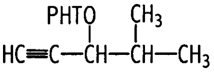
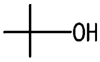
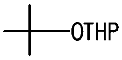
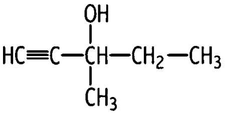
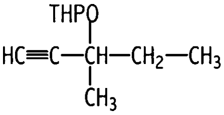
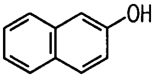
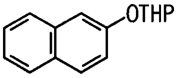
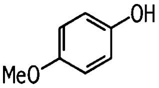
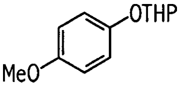
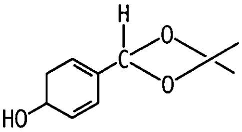
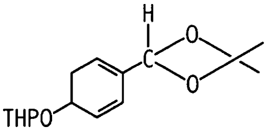
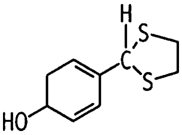
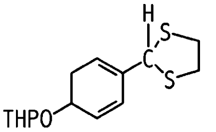
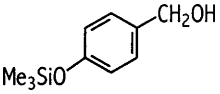
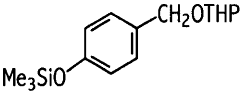
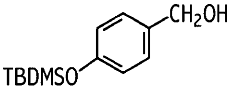
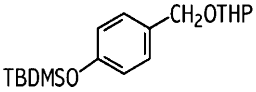
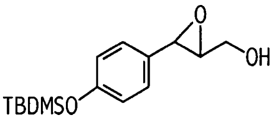
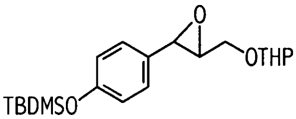
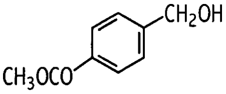
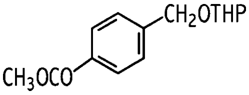
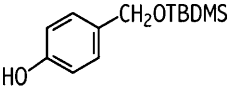
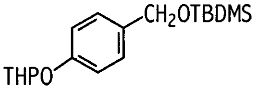
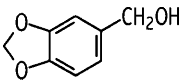
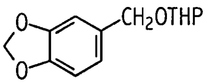
Treatment of 3,4-dihydro-2*H*-pyran with benzyl alcohol (**1a**) in dichloromethane in the presence of anhydrous calcium chloride for 1.5 h at ambient temperature afforded 2-benzyl tetrahydropyranyl ether **2a** in 89% yield. The reaction was extended to a variety of alcohols (primary, secondary, tertiary, allylic, benzylic, propargylic) and phenols which also underwent facile tetrahydropyranylation with anhydrous $CaCl_2$ in CH_2Cl_2 at ambient temperature, affording the corresponding tetrahydropyranyl ethers **2a**–**2t** in good to excellent yields. Even otherwise less reactive tertiary alcohols gave the corresponding *THP* ethers **2i**, **j** in good yield. It is worth commenting that sensitive functional groups such as C=C (**1c**, **g**), C≡C (**1h**, **j**), methoxy (**1l**), acetal (**1m**), thioacetal (**1n**), *TMS* (**1o**), *TBDMS* (**1p**), epoxide (**1q**), acetyl (**1r**), or methylenedioxy (**1t**) remained intact under these neutral and mild reaction conditions (Table 1). When tetrahydropyranylation of alcohols was tried without anhydrous calcium chloride, it resulted in isolation of unreacted alcohols even after stirring for extended periods (12 h). Attempts to remove the

Table 1. Tetrahydropyranylation of alcohols and phenols using anhydrous $CaCl_2$

	Substrate (**1**)	Product (**2**)	t/h	Yield/%^{a,b}	Ref.^{c}
a			1.5	89	[2, 4]
b	$CH_3(CH_2)_5$—OH	$CH_3(CH_2)_5$—OTHP	2	92	[2, 4]
c			2.5	78	[2, 4]
d			2	85	[2, 4]
e			2	85	[2, 4]
f			2.5	83	[2, 4]
g			3	67	[2, 4]

(*continued*)

Table 1 (*continued*)

	Substrate (**1**)	Product (**2**)	t/h	Yield/%[a,b]	Ref.[c]
h	 $HC\equiv C-\overset{OH}{CH}-\overset{CH_3}{CH}-CH_3$	 $HC\equiv C-\overset{PHTO}{CH}-\overset{CH_3}{CH}-CH_3$	1.5	75	[2, 4]
i			4.5	80	[2, 4]
j	 $HC\equiv C-\underset{CH_3}{\overset{OH}{CH}}-CH_2-CH_3$	 $HC\equiv C-\underset{CH_3}{\overset{THPO}{CH}}-CH_2-CH_3$	2	80	[2, 4]
k			1	89	[2, 4]
l			0.5	87	[2, 4]
m			1	87	[2, 4]
n			1.5	95	[2, 4]
o			2	91	[2, 4]
p			1.5	94	[2, 4]
q			3	84	[2, 4]
r			3	93	[2, 4]
s			2.5	88	[2, 4]
t			1.5	93	[2, 4]

[a] Yields of pure isolated products; [b] products characterized by spectroscopic data; [c] references for spectroscopic data of products

THP group using the same catalyst in methanol at 25°C or reflux temperature (65°C) failed.

Attempts to effect tetrahydropyranylation of alcohols using catalysts such as NaCl, KCl, or $CoCl_2$ failed. However, *Lewis* acids such as $ZnCl_2$ and LiCl are useful to some extent as catalysts for the preparation of *THP* ethers. Considering recently reported results on the tetrahydropyranylation of alcohols using lithium perchlorate [6], the present protocol is superior in terms of cost, yields, and reaction times. *t*-Butanol in diethyl ether with lithium perchlorate as catalyst afforded the corresponding *THP* ether in 56% yield within a period of 17 h, whereas the *THP* ether of the same alcohol was obtained in 80% yield in 4.5 h using anhydrous calcium chloride. In this case, the advantage lies in the neutral reaction conditions which restrict dehydration of the alcohol as compared to the weakly acidic conditions of lithium perchlorate in diethyl ether. Benzyl alcohol and cyclohexanol gave the corresponding *THP* ethers in excellent yields in 1.5 h and 2.5 h with $CaCl_2$, whereas the lithium perchlorate pathway required 12 h for the same reaction.

In conclusion, anhydrous calcium chloride has been found to be an excellent inexpensive catalyst for the protection of alcohols and phenols as *THP* ethers under neutral and mild conditions (room temperature).

Experimental

IR spectra were recorded on a Bomem MB-104 FTIR spectrometer, ^1H NMR spectra on a Bruker AC-300 F NMR spectrometer operating at 300 MHz using $CDCl_3$ as solvent and *TMS* as internal standard.

General procedure for the preparation of THP ethers

A mixture of 3,4-dihydro-2*H*-pyran (7 mmol) and 5 mmol of alcohol was stirred at 25°C in the presence of 1 mmol anhydrous $CaCl_2$ in 5 cm^3 CH_2Cl_2. After completion of the reaction (*TLC*), the catalyst was filtered off and washed with $3 \times 5\,cm^3$ CH_2Cl_2. The solvent was removed under vacuum, and the product was further purified by column chromatography on silica gel (hexane:ethyl acetate = 9:1). The products were identified by TLC, elemental analyses, and spectroscopic data [2, 4].

Acknowledgments

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