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Mild and efficient tetrahydropyranylation of alcohols and dehydropyranylation of THP ethers catalyzed by ferric perchlorate

Majid M. Heravi,* Farahnaz K. Behbahani, Hossien A. Oskooie and Rahim Hekmat Shoar

Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran 1234, Iran

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Abstract—A simple, mild and efficient method for tetrahydropyranylation and dehydropyranylation of alcohols in the presence of ferric perchlorate are described.

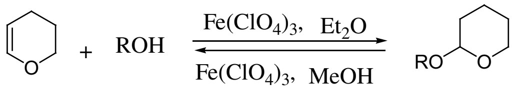
1. Introduction

The protection–deprotection of hydroxyl groups is of paramount importance in multi-step organic synthesis. THP ethers are one of the most useful protective groups in multi-stage synthesis, because they are stable under neutral and basic conditions, and resistant to oxidizing and reducing agents.[1] THP ethers can be easily prepared from a variety of hydroxyl containing compounds with 3,4-dihydro-2*H*-pyran (DHP). Some efficient and commercially available reagents[2] and some readily available naturally occurring clays[3] have been utilized as efficient and versatile catalysts for this interconversion. Very recently, the reaction was performed using acetonyl triphenyl phosphonium bromide supported on polystyrene.[4] Deprotection of THP ethers for regeneration of hydroxyl compounds usually entails rather harsh acidic conditions, which are rarely compatible with sensitive substrates.[5]

In recent years, ferric perchlorate has gained importance as a versatile reaction medium for effecting various organic transformations such as regio and stereoselective alcoholysis and hydrolysis of epoxides,[6] transformation of allylic and benzylic ethers[7] and synthesis of amides from benzylic alcohols.[8] Ferric perchlorate is a hygroscopic compound, which is readily prepared by the reaction of ferric hydroxide and perchloric acid, and can be stored for a long time in a desiccator. It is non-toxic, inexpensive and soluble in most of the organic solvents, and is not explosive even when heated in solution. In line with the continuing interest, in this communication we wish to report that ferric perchlorate is also an excellent and efficient catalyst to perform tetrahydropyranylation in Et_2O and deprotection in MeOH at room temperature (Scheme 1).

The mild, facile, high yielding and homogeneous reaction conditions applied for tetrahydropyranylation and the easy work up procedure ensures an efficient rout and provides an attractive and variable alternative to the previously reported procedure for protection of hydroxyl groups as THP ethers. In addition to tetrahydropyranylation by changing of solvent to methanol the reverse process, that is, deprotection, is also brought about with similar ease, is high yielding and effective.

All types of alcohols (primary, secondary, tertiary, benzylic, allylic and propargylic) were easily converted to THP ethers by the treatment of 3,4-dihydro-2*H*-pyran with catalytic amounts of ferric perchlorate in Et_2O at an ambient temperature (Table 1). Of various phenols studied, only phenol itself furnished THP ether with low yield whereas substituted phenols either with electron withdrawing or electron-releasing substituent did not react at all.



Scheme 1.

Keywords: Protection; Deprotection; Alcohols; Tetrahydropyranylation; Ferric perchlorate.

* Corresponding author. Tel.: +98 218041347; fax: +98 218047861; e-mail: mmh1331@yahoo.com

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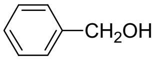
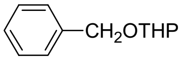
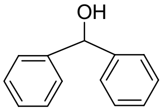
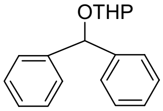
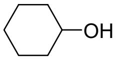
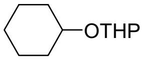
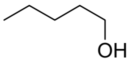
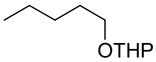
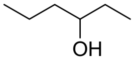
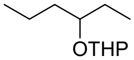
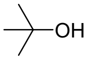
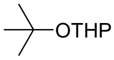
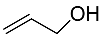
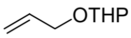
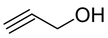
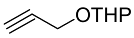
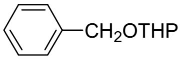
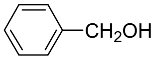
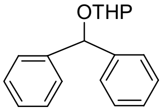
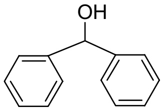
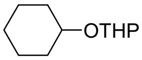
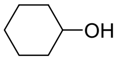
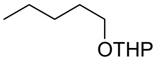
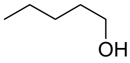
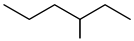
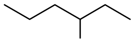
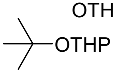
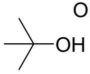
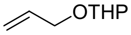
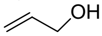
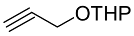
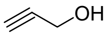
Table 1. Ferric perchlorate catalyzed tetrahydropyranylation of hydroxyl compounds in Et_2O

Entry	Hydroxyl compound	Time (h)	Product	Yield[a] (%)
1		1.5		98
2		2.5		75
3		2		94
4		1.5		98
5		2.5		90
6		3		92.5
7		1.5		85
8		1		96

[a] Yields refer to GC analysis.

Table 2. Deprotection of THP ethers catalyzed by ferric perchlorate in MeOH

Entry	THP ether	Time (min)	Product	Yield[a] (%)
1		120		92
2		75		87
3		90		89
4		90		92
5		45		94
6		90		82
7		120		92
8		90		93

[a] Yields refer to GC analysis.

It is worth mentioning that ferric perchlorate did not affect the double bond or triple bond of allylic and propargylic alcohols (entries 7 and 8). Under acidic conditions, tertiary alcohols (entry 6) are known to undergo dehydration.[9] Ferric perchlorate could be applied to catalyze the protection and deprotection of this compound perfectly (Tables 1 and 2, entry 6). It is noteworthy that under these conditions no oxidation of alcohols and even benzylic alcohols (Tables 1 and 2, entry 1) is observed. Although Fe(III) reagents are known to be strong oxidants,[10] Fe(III) of ferric perchlorate, in this reaction behaves solely as a powerful and highly selective Lewis acid. The oxidation potential of ferric perchlorate in methanol is only 0.70v.[11] The reactions occur under essentially neutral conditions and are particularly well suited for acid labile substrates.

The deprotection of THP ethers can be carried out under similar mild reaction conditions and with the same ease as the protection process. The results of the selected examples are illustrated in Table 2.

In summary, we have developed ferric perchlorate as an excellent catalyst for protection and deprotection of hydroxyl groups in different medium under mild conditions. In addition, the reactions are high yielding and easy to work up. Due to the catalytic nature of the reaction, mildness, non-toxic nature, neutrality of the condition, availability and the low cost of the reagent, we believe it would be a useful addition to the available organic methodologies.

2. Experimental

All products were known and their analytical and spectral data were compared with those of authentic samples.

2.1. Protection of hydroxy compounds catalyzed by ferric perchlorate. Typical procedure

Ferric perchlorate (0.0712 g, 0.154 mmol) in Et_2O (1 mL), DHP(0.42 g, 5 mmol) and benzyl alcohol (0.54 g, 5 mmol) were mixed at room temperature for 1.5 h. The progress of the reaction was monitored by TLC (eluent, *n*-hexane–ether, 4:1). Upon completion, the reaction mixture was passed through a short column of silica gel using petroleum ether as an eluent. The solvent was evaporated to dryness to afford pure benzyl THP ether in 98% yield.

2.2. Deprotection of THP ethers catalyzed by ferric perchlorate. Typical procedure

$Fe(ClO_4)_3$ (0.0712 g, 0.154 mmol) and benzyl THP ether (0.96 g, 5 mmol) were stirred in MeOH (2 mL) at room temperature for 45 min. The progress of the reaction was monitored by TLC (eluent, *n*-hexane–ether, 4:1). After completion of the reaction, the mixture was passed through a short silica gel pad. The solvent was evaporated off to afford pure benzyl alcohol in 92% yield.

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