Anhydrous FePO₄ as a Cost-Effective and Recyclable Catalyst for Tetrahydropyranylation and Tetrahydrofuranylation of Alcohols and Phenols

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Abstract: In this article, a mild and efficient protocol for the tetrahydropyranylation and tetrahydrofuranylation of various aliphatic and benzylic alcohols and phenols into their corresponding THP and THF ethers (with 3,4-dihydro- 2H-pyran, DHP and 2,3-dihydrofuran, DHF) has been developed using a catalytic amount of anhydrous $FePO_4$ at room temperature and relatively short reaction times in good to excellent yields.

Keywords: Alcohols, anhydrous FePO₄, deprotection, phenols, protection, THF ethers, THP ethers.

INTRODUCTION

The protection-deprotection of hydroxyl groups is preeminent importance in multi-step organic synthesis. THP ethers are one of the most useful protective groups in multistage synthesis, due to the remarkable stability under neutral and basic conditions, and are resistant to oxidizing and reducing agents such as hydrides, alkylating reagents, Grignard reagents and organometallic reagents [1]. Their sensitivity to acidic deprotection allows orthogonal protecting groups strategies to be employed [2] but their couse with other acid-sensitive groups remains problematic. The structurally similar but less described tetrahydrofuranyl ethers (using 2,3-dihydrofuran, DHF) are also important and have been utilized in hydroxyl groups' protection [3].

THP ethers can be extensively prepared from a variety of hydroxyl containing compounds with 3,4-dihydro-2H-pyran (DHP). Recently, a remarkable advance in catalysts used for the tetrahydropyranylation of alcohols and phenols has been reported. These include I₂ [4], zeolite [5], water [6], PdCl₂ (CH₃CN)₂ [7], trichloroisocyanuric acid (TCCA) [8], Bi(OTf)₃.4H₂O [9], SnCl₂.H₂O [10], H₁₄[NaP₅W₃₀O₁₁₀] [11], 2,4,6-trichloro[1,3,5]triazine [12], Fe(HSO₄)₃ [13],

Benzyltriphenylphosphonium tribromide [14], Fe(ClO₄)₃ [15], Al(OTf)₃ [16], I₂-insitu (Fe(NO₃)₃ · 9 H₂O/NaI) [17], copper nitrate/acetic acid [18], copper *p*-toluenesulfonate/ acetic acid [19], acetyl chloride [20], activated carbon supported sulfuric acid [21] and boric acid [22], whereas THF ethers were achieved using the p-TsCl/NaH/THF system [23], CrCl₂ [24], ceric ammonium nitrate [25] and recently with alkylperoxy- λ^3 -iodane [26]. Most of these are proved to be efficient for organic reactions. However, some of these methods have several drawbacks such as harsh reaction conditions (extreme pH, high reaction temperature), expensive catalysts or low reactivities. In addition, some of these catalysts cannot be recovered and reused.

Deprotection of THP ethers for regeneration of hydroxyl compounds usually entails rather harsh acidic conditions which are rarely compatible with sensitive substrates [7].

In recent years, anhydrous $FePO_4$ has gained importance as versatile reaction medium for effectting various organic transformations sush as selective oxidation of CH₄ to CH₃OH [27] and benzene to phenol [28], one-pot synthesis of dihydropyrimidinones and thiones [29] and synthesis of triarylated imidazoles [30] as a catalyst. In this communication we wish to report that anhydrous FePO₄ is also excellent and efficient catalyst to perform tetrahydropyranylation/tetrahydrofuranylation in dichloromthane and deprotection in methanol at room temperature (Scheme 1).

$$ROH + \bigcup_{O} \text{ or } \bigcup_{O} \frac{FePO_4/CH_2Cl_2}{FePO_4/MeOH} RO \longrightarrow_{O} \text{ or } RO \longrightarrow_{O}$$

Scheme 1.

RESULTS AND DISCUSSION

In our first efforts for preparation of THP ethers we treated benzyl alcohol with DHP and 2 mol% of $FePO_4$ under solvent-free conditions. The desired THP ether was formed in low yield and found that the transformation was very slow under solvent-free conditions. However, several solvents were examined to standard reaction conditions (Table 1) and dichloromethane (DCM) as a solvent was chosen for the reaction at room temperature (entry 5, Table 1) that ensured clean conversion to the desired THP ether in high yield.

Treatment of various other alcohols and phenols in this way (Table 2) provided efficient access to the THP ethers. The protection is useful for primary and secondary alkanols as well as a range of phenols and is highly efficient in DHP and DHF due to just 1.1 equiv of these reagents are used per OH group.

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Table 1.	Varying of the Solvents for	Preparation of 2-(benzyloxy)-tetrahydro-2H-pyran
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Entry	Solvent	Time (h)	Yield (%) ^a
1	Solvent free	24	15
2	Diethyl ether	24	35
3	Carbon Tetrachloride	12	40
4	Toluene	24	30
5	Dichloromethane	4.0	90

^aYields refered to GC.

Table 2. Conversion of Alcohols and Phenols into their Corresponding THP and THF Ethers Using Anhydrous FePO₄. All Reactions were Conducted in DCM and all Reaction Times were Determined by TLC(Conversion 100%)

Entry	Substrate	Product Time (h)		Yield (%) ^a
1	ОН	ОТНР	4.0	90
2	OH	OTHP	6.0	81
3	OH O	OTHP O	7.0	86
4	OH	OTHP	5.5	96
5	ОН	OTH₽	2.5	80
6	ОН	OTHP	3.0	92
7	≫∽ _{OH}	OTHP	4.0	97
8	OH	OTHP	4.0	90
9	О	ООТНР	8.0	95
10	но	THPO	8.0	92
11	OH	OTHP	6.0	83
12	ОН	OTHP	2.0	88

(Table 2)	. Con	ıtd
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Entry	Substrate	Product	Time (h)	Yield (%) ^a
13	ОН	OTHF	5.0	80
14	ОН	OTHF	4.5	82
15	ОН	OTHF	2.0	90
16	но	THFO	8.0	84
17	ОН	OH OTHP	3.0	85

^aYields referred to GC.

All types of alcohols (primary, secondry, tertiary, benzylic, allylic and propargylic) were easily converted to THP/THF ethers by treatment of 3,4-dihydro-2H-pyran and 2,3-dihydrofuran with catalytic amounts of anhydrous $FePO_4$ in DCM at ambient temperature (Table 2).

Accordingly, primary and secondary benzyl alcohols undergo tetrahydropyranylation in 81-90 yields (entries 1-3, Table 2). In addition to benzylic alcohols, this catalyst is effective for the variety of aliphatic alcohols (entries 4-6, 12, 15; Table 2). Primary alcohols protected within less time than secondary and tertiary alcohols. The longer reaction time could be due to the steric effect exerted by bulky groups. It is very interesting to note that tertiary and secondary alcohols such as t-butanol can also be protected with satisfactory yield and there was no elimination product in the reaction mixture.

Of various naphthols studied, only 2-naphthol furnished THP ether with high yield where as substituted naphthols either with electron withdrawing or electron-releasing substituent did not react at all. In order to survey chemoselectivity of this transformation, 3-, 4-hydroxy benzaldehydes were subjected as substrates. It was found that C=O group was not involved in reaction and remain intact (entries 9, 10, Table 2). FePO₄ also did not affect on either double or triple bond of allylic and propargylic alcohols (entries 7 and 8) and could be perfectly used to catalyze the protection and deprotection of aliphatic alcohols where as dehydration of aliphatic alcohols was reported under acidic condition [31] (entry 4-6, Table 2). It is noteworthy that under these conditions no oxidation of alcohols and even benzylic alcohols (entry1) was observed. Although FePO₄ has been known as oxidant to convert CH₄ to CH₃OH [15], in this reaction behaves solely as a powerful and highly selective Lewis acid. As a natural product, menthol was subjected in this reaction and afforded the corresponding THP ether in high yield (entry 15, Table 2). In the end, THP ethers on primary alcohol groups were selectively formed from dihydroxy alcohols(entry 17, Table 2).

The deprotection of THP ethers can be carried out under similar mild reaction conditions and with the same ease as the protection process in good to excellent yields. The results of the selected examples are illustrated in Table **3**.

Although there are several reports on the formation of THF ethers, to the best of our knowledge rarely of the reported protocols involve Lewis acid catalysts [16]. The broader generality of our method was thus explored by successfully synthesizing THF ethers. The alcohols listed in Table **2** were treated under the standard conditions described above to produce the corresponding THP ethers.

In order to show the merits of this catalytic method in comparison with those of reported protocols, we compiled the results of the formation of 2-(benzyloxy)-tetrahydro-2*H*-pyran (Entry 1, Table 2) in the presence of a variety of iron (III) salts and complexes. From the results given in Table 4, the advantages of our method are evident, regarding the catalyst amounts, heterogeneous and recyclable of the catalyst, a lack of the nitrate and perchlorate (entry 1, 3; Table 4) and shorter reaction time (entry 4) which are very important in chemical industry and from green chemistry point of view especially when it is combined with easy separation.

EXPERIMENTAL

Protection of hydroxy Groups Catalyzed by FePO₄. Typical Procedure

Ferric phosphate (0.015 g, 2.0 mol%) in DCM (1 ml), DHP (0.46 g, 5.5 mmol) and benzyl alcohol (0.54 g, 5 mmol) were mixed at room temperature. The progress of the reaction was monitored by TLC (eluent: n-hexane:ethylacetate, 4:1). Upon completion of the reaction, mixture of the reaction was passed through of silica gel and washed using n-hexane as an eluent. After drying and evaporating of solvent, the product obtained in high yield and physical and spectroscopy data compared with those of authentic samples.

Entry	Substrate	Product	Product Time (h)		
1	OTHP	ОН	4.0	94	
2	OTHP	OH	2.5	91	
3	OTHP O	OH OH	3.0	82	
4	OTHP	ОН	4.0	90	
5	OTHP	ОН	2.0	80	
6	ОТНР	ОН	3.0	85	
7	OTHP	NOH	2.5	86	
8		OH	2.0	84	
9	OTHP		2.0	88	
10	OOTHP	О	4.0	81	
11	THPO	но	4.0	80	
12	OTHP	OH	3.0	92	
13	OTHF	ОН	4.0	90	
14	OTHF	Он	4.0	85	

Table 3. Deprotection of THP and THF Ethers Using Anhydrous FePO ₄ . All Reactions were Conducted in M	Iethanol
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^aYields referred to GC.

Table 4. Comparison the Effect of Varying iron (III) Salts in Preparation of 2-(benzyloxy)-tetrahydro-2H-pyran

Entry	Catalyst	Catalyst (mol%)	Time (h)	Solvent	Yield (%)	Ref.
1	Fe(ClO ₄) ₃	3.0	1.5/r.t	Et ₂ O	98	[15]
2	Fe ₂ (SO ₄) ₃ .X H ₂ O	1.0	1.0/r.t	-	95	[32]
3	Fe(NO ₃) ₃ .9H ₂ O/ Na I	1.5/2.6	5.0/r.t	DCM	96	[32]
4	FeCl ₃ .6H ₂ O / Na I	-	12/ r.t	DCM	95	[18]
5	FePO ₄	2.0	5.0/ r.t	DCM	93	This work

Deprotection of THP Ethers Catalyzed by FePO₄. **Typical Procedure**

Ferric phosphate (0.015 g, 2.0 mol%) and benzyl THP ether (0.96g, 5.0 mmol) were stirred in MeOH (2 ml) at room temperature. The progress of the reaction was monitored by TLC (eluent, n-hexane:diethylether, 4:1). After the completion of the reaction, DCM (5.0 ml) was added and catalyst was filterated off. Evaporating of the solvent resulted corresponding hydroxyl group compounds in high vield.

CONCLUSION

In summary, we have developed iron (III) phosphate as a versatile and an excellent catalyst for both protection and deprotection of THP and THF ethers 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.

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