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Mild and Efficient Tetrahydropyranylation and Deprotection of Alcohols Catalyzed by Heteropoly Acids

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Abstract: *A simple, mild and effective method to form 2-tetrahydropyranyl ethers of alcohols and phenol and the removal of this protective group in the presence of heteropoly acids as catalysts are described.*

Tetrahydropyranylation is one of the most useful methods to protect alcoholic and phenolic hydroxyl groups due to the stability of the resulting 2-tetrahydropyranyl ethers. They are resistant to oxidizing and reducing agents and unreactive under neutral and basic conditions which makes tetrahydropyranylation the method of choice in natural product synthesis.[1] Even though that numerous electrophilic catalysts were shown to be effective in forming tetrahydropyranyl ethers by the reaction of alcohols and phenols with 3,4-dihydro-2*H*-pyran new reports are still being published disclosing the use of new reagents. Alumina impregnated with $ZnCl_2$[2], Envirocat EPZG® (an environmentally friendly supported reagent)[3] and dicyanoketene ethylene acetal[4] have recently been described to be effective exhibiting some new advantageous properties. Tetrahydropyran was also found to react with alcohols to form 2-tetrahydropyranyl ethers under oxidative conditions.[5]

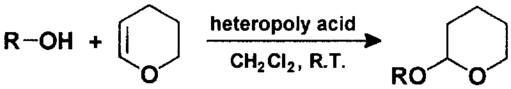
In line with this continuing interest we now wish to report that heteropoly acids are also excellent and effective catalysts to perform tetrahydropyranylation under mild conditions. Due to their acidic and redox properties heteropoly compounds (heteropoly acids and their salts) are useful and versatile catalysts in a number of transformations.[6] Since they exhibit weak superacidic properties they can be used in reactions requiring electrophilic catalysis. They have also been proven to be equally good catalysts in various oxidations. They are applied in bulk or supported forms, and both homogeneous and heterogeneous catalysis are possible.

The mild, homogeneous reaction conditions applied for tetrahydropyranylation and the easy workup ensure an effective synthesis and provide an attractive and viable alternative to the known protection of various hydroxyl compounds. In addition to tetrahydropyranylation the reverse process, that is deprotection, is also brought about with similar ease and effectiveness.

Four heteropoly acids ($H_3[PMo_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, $H_3[PW_{12}O_{40}]$, $H_4[SiMo_{12}O_{40}]$)[7] were at first tested in the tetrahydropyranylation of benzyl alcohol and all were found to catalyze the transformation. Further systematic studies were carried out with $H_3[PW_{12}O_{40}]$ (abbreviated as PW) which is the strongest and $H_4[SiMo_{12}O_{40}]$ (SiMo) which is the weakest acid of the four.

All types of alcohols (primary, secondary, tertiary, benzylic, allylic) undergo facile tetrahydropyranylation to form tetrahydropyranyl ethers in high yields (Table 1). The least reactive *terc*-amyl alcohol requires prolonged reaction time (entry 9). Of various phenols studied only phenol furnished the tetrahydropyranyl ether with satisfactory yield (entry 10), whereas substituted compounds either with electron-withdrawing or electron-releasing substituent reacted sluggishly to give products with low yields.

Table 1. Tetrahydropyranylation of alcohols catalyzed by $H_3[PW_{12}O_{40}]$ (PW) and $H_4[SiMo_{12}O_{40}]$ (SiMo)



Entry	Alcohol	Time	Yield (%)[a] PW	SiMo
1	1-Octanol	30 min	88	88
2	1-Decanol	30 min	92	83
3	Isobutyl alcohol	30 min	96	94
4	Tetrahydrofurfuryl alcohol	2 h	84(63)[b]	72
5	Benzyl alcohol	30 min	90(73)[b]	76
6	2-Octanol	30 min	80	90
7	Cyclopentanol	30 min	92(80)[b]	92
8	Cyclohexanol	30 min	84	83
9	*terc*-Amyl alcohol	4 h	93	93
10	Allyl alcohol	30 min	96	96
11	Phenol	30 min	64	80

[a] GC yields. [b] Isolated yields.

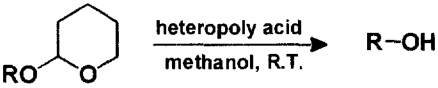
All tetrahydropyranyl ethers are known compounds and were characterized by comparison with authentic samples by means of IR and ^{1}H NMR.

In a typical procedure 3,4-dihydro-2*H*-pyran (30 mmol, 2.52 g) dissolved in CH_2Cl_2 (5 ml) was added to a stirred solution of benzyl alcohol (20 mmol, 2.16 g) and $H_4[PW_{12}O_{40}]$ (0.02 mmol, 0.056 g) in CH_2Cl_2 (25 ml) at ambient temperature for 5 min. Stirring was continued for an additional 30 min (or as required according to GC[8]). The solution was first filtered through a short column of basic alumina[9] then silica gel, washed with a small amount of CH_2Cl_2 and concentrated to give the pure tetrahydropyranyl ether (2.8 g, 73%).

The removal of the protective tetrahydropyranyl group can be carried out under similar mild reaction conditions and with the same ease as the protection process. The results of selected examples collected in Table 2 indicate that the efficiency of the heteropoly acid catalyzed deprotection is also highly satisfactory.

In a typical deprotection reaction the solution of the 2-tetrahydropyranyl ether of benzylic alcohol (10 mmol, 1.92 g) and $H_4[PW_{12}O_{40}]$ (0.02 mmol, 0.056 g) in methanol (10 ml) was stirred at ambient temperature for 30 min. After a work-up identical to that used in tetrahydropyranylation pure benzylic alcohol was isolated (0.79 g, 73%).

Table 2. Deprotection of tetrahydropyranyl ethers of alcohols catalyzed by $H_3[PW_{12}O_{40}]$



Entry	R in tetrahydropyranyl ether	Time	Yield (%)[a]
1	1-Octyl	4 h	90
2	1-Decyl	4 h	94
4	Tetrahydrofurfuryl	4 h	90[b]
5	Benzyl	4 h	73[b]
6	2-Octyl	2 h	85
7	Cyclopentyl	4 h	84[b]
8	Cyclohexyl	30 min	93
9	Phenyl	30 min	71

[a] GC yields. [b] Isolated yields.

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8 Carlo Erba Fractovap Mod G equipment, thermal conductivity detector, 15% SE 52 on Kieselguhr column (1.2 m), hydrogen carrier gas.

9 Basic alumina is prepared by thoroughly mixing 1000 g alumina with 20 ml 5M NaOH. The mixture is allowed to stand for a few days with frequent shaking.

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