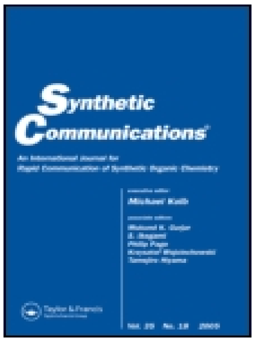

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Efficient Tetrahydropyranylation of Phenols and Alcohols Catalyzed by Supported Mo and W Keggin Heteropolyacids

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ABSTRACT

The protection of phenols as tetrahydropyranyl acetals is studied using supported Keggin heteropolyacids as catalysts, specifically

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molybdophosphoric or tungstophosphoric acids supported on silica. Phenol tetrahydropyranyl acetals are obtained in short times at room temperature with excellent yields. Protection of alcohols is also performed under mild conditions using both supported heteropolyacids, with yields ranging between good and quantitative. The reactions are clean and their workup is very simple. The use of these solid catalysts allows replacing the usual soluble inorganic acids, contributing to waste reduction.

Key Words: Protecting group; Tetrahydropyranyl; Heteropolyacids; Keggin catalyst; Alcohols; Phenols.

INTRODUCTION

Transformation of phenols and alcohols into their mixed acetals, ketals, ethers, or esters, has been recognized as a useful method for hydroxyl group protection.[1] Tetrahydropyranyl acetal is one of the most common and useful derivatives for that protection, because of its ease of formation, relative ease of removal, stability of the acetals to various nonacidic reaction conditions and the reagent low cost. Introduction of THP group on oxygen is usually carried out using a mineral acid as catalyst both in liquid phase[1,2] or adsorbed on a solid support.[3] Besides, other heterogeneous catalysts have been used, such as zinc chloride on alumina,[4] vanadyl(IV) acetate,[5] zirconium sulfophenyl phosphonate,[6] etc. The problems associated with both, the handling and the disposal of the conventional inorganic acids e.g., sulfuric, hydrofluoric, boron trifluoride have raised the interest in the development of alternative clean processes using solid acid catalysts.

Keggin heteropolyacids (HPAs) are constituted by a close-packed framework of metal-oxygen octahedra, MO_6 ($M = Mo(VI), W(VI)$) surrounding a central atom X (Si(IV), P(V)).[7] These catalysts are stronger acids than the conventional ones. Advantages of using supported HPAs to be highlighted are their ease of recovery and recycling after carrying out the liquid phase reactions, and the easier isolation of the products in comparison with homogeneously catalyzed reactions. The preparation of supported Keggin based catalysts from tungstophosphoric acid (TPA) and from molybdophosphoric acid (MPA) has been described elsewhere.[8–10] A variety of reactions have been reported to be catalyzed by HPAs.[7,11,12] Tetrahydropyranylation of alcohols was carried out using homogeneous catalysis by HPAs, and likewise was accomplished the protection of unsubstituted phenol; however, tetrahydropyranylation of substituted phenols was reported to proceed with low yields.[12] The use of other acid catalysts for achieving the protection of phenols has involved reaction conditions such as e.g., stirring of a mixture of the reactants and a saturated AcOEt solution of HCl for 24 h at 25°C.[13]

RESULTS

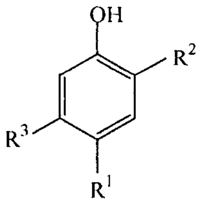
We have found that tetrahydropyranylation can be accomplished very easily and cleanly on phenols, as well as on naphthols (Table 1). Toluene was used as solvent and both HPAs supported on silica, MPA/S and TPA/S, were used as catalysts. Reactions were optimized by varying reaction temperature, reaction time, MPA(TPA) content of the catalyst, mole ratio MPA/S(TPA/S):ArOH, 3,4-dihydro-2*H*-pyran (DHP) excess and solvent. Characteristic reaction conditions include short times and room temperature. In all the experiments the desired products were obtained free of secondary products and almost quantitatively, and starting phenol was quantitatively recovered when the reaction was incomplete. Optimized reaction conditions are showed in Table 1 and the structures of the phenols are included in the Figure 1. Besides, we have applied the same procedure for achieving the tetrahydropyranylation of some alcohols in toluene, comparing catalysis by both supported HPAs (Table 2).

Table 1. Protection of phenols and naphthols as tetrahydropyranyl acetals.[a]

Phenol	Catalyst	Time (h)	Mole ratio DHP/phenol	% Yield[b]
1	MPA/S	1	2:1	93
1	TPA/S	1	2:1	93
1	MPA/S	1	5:1	96
2	MPA/S	5	2:1	75
2	MPA/S	2	5:1	97
3	MPA/S	1	2:1	89
4	MPA/S	1	2:1	93
5	MPA/S	2	2:1	90
6	MPA/S	2	2:1	89
7	MPA/S	1	2:1	92
8	MPA/S	1	2:1	89

[a] Reactions were performed at 20°C in toluene, using 1% (mmol) of MPA (TPA) supported on silica and washed.[14]

[b] Yields were calculated from isolated products.



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Compound	*R*^{1}	*R*^{2}	*R*^{3}
1	H	H	H
2	NO_2	H	H
3	OMe	H	H
4	Cl	H	H
5	CHO	OMe	H
6	H	*i*-Pr	Me
7	α-Naphthol		
8	β-Naphthol		

Figure 1. Phenol substrates for the tetrahydropyranylation reaction.

Table 2. Protection of alcohols as tetrahydropyranyl acetals.[a]

Compound	Alcohol	Catalyst	% Yield[b]
9	Benzyl	MPA/S	98
9	Benzyl	TPA/S	97
10	2-Phenylethanol	MPA/S	97
10	2-Phenylethanol	TPA/S	100
11	3-Phenyl-1-propanol	MPA/S	89
11	3-Phenyl-1-propanol	TPA/S	88
12	1-Phenyl-2-propanol	MPA/S	94
12	1-Phenyl-2-propanol	TPA/S	93
13	2-Phenoxyethanol	MPA/S	96
13	2-Phenoxyethanol	TPA/S	97

[a] Reactions were performed for 1 h at 20°C in toluene, using a mole ratio alcohol:DHP (1:2) and 1% (mmol) of MPA (TPA) supported on silica and washed.[14]

[b] Yields were calculated from isolated products.

When unsubstituted phenol (**1**) was protected using a DHP:**1** mole ratio 1:1, toluene as solvent and 1% MPA/S as catalyst, a maximum yield of 82% was attained at 1 h reaction at 15°C. A reaction time of 0.5 h was insufficient, and reaction times exceeding 1 h gave a lower yield. Besides, no noticeable changes occur by increasing the amount of the catalyst to 5%, irrespective of the temperature. A 93% yield was obtained at 20°C and 1 h reaction using both catalysts (MPA/S or TPA/S), mole ratio 2:1, and toluene as solvent (Table 1). *p*-Nitrophenol (**2**) required 5 h at 20°C for attain a maximum yield, however using four-fold molar excess DHP, an excellent yield is achieved in 2 h. THP acetals of compounds **3–8** are obtained in good yield in 1–2 h reaction (Table 1). Alcohols were protected in good to quantitative yield irrespective of the used catalyst (Table 2). Obtained THP acetals were homogeneous by HPTLC and their microanalytical[15] and spectral data agree with the expected values.

On reutilization of the catalyst once more, the results obtained in the first use were reproduced, within the experimental error.

REPRESENTATIVE PROTECTION REACTION

Protection was carried out mixing the phenol (0.33 mmol) with the stated quantity of DHP (see Table 1), the supported catalyst[14] and toluene (1 mL). The suspension was stirred at 15 or 20°C during the stated time (Table 1) and then was stirred with 3 mL of toluene; the catalyst was filtered off and then was washed twice with 1 mL portions of toluene. The extract and washings were combined and the organic phase was washed with 1 M NaOH, then it was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was then subjected to a short column flash chromatography, eluting the product with toluene. Protection of alcohols does not involve the alkaline washing step.

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each, with continuous stirring. The final content of HPA showed to be 0.3 mg MPA(TPA)/mg of catalyst.

15. Analytical data for selected acetals: **1**—THP: Calcd. for $C_{11}H_{14}O_2$: C, 74.13, H, 7.92. Found: C, 74.01, H, 7.90. **2**—THP: Calcd. for $C_{11}H_{13}NO_4$: C, 59.19, H, 5.87, N, 6.27. Found: C, 59.23, H, 5.85, N, 6.24. **4**—THP: Calcd. for $C_{12}H_{16}O_3$: C, 69.21, H, 7.74. Found: C, 69.16, H, 7.72. **5**—THP: Calcd. for $C_{15}H_{22}O_2$: C, 76.87, H, 9.48. Found: C, 76.81, H, 9.44. **8**—THP: Calcd. for $C_{15}H_{16}O_2$: C, 78.92, H, 7.06. Found: C, 78.87, H, 7.03. **10**—THP: Calcd. for $C_{13}H_{18}O_2$: C, 75.69, H, 8.80. Found: C, 75.62, H, 8.78. **11**—THP: Calcd. for $C_{14}H_{20}O_2$: C, 76.32, H, 9.15. Found: C, 76.25, H, 9.12. **13**—THP: Calcd. for $C_{13}H_{18}O_3$: C, 70.24, H, 8.16. Found: C, 70.19, H, 8.12.

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