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JSCS–4268 *Short communication*

SHORT COMMUNICATION

Catalytic tetrahydropyranylation of phenols and alcohols using vanadium(V)-substituted polyoxomolybdates

ALI GHARIB[1,2]* and MANOUCHEHR JAHANGIR[1]

[1]*Department of Chemistry, Islamic Azad University, Mashhad, Iran and*
[2]*Agricultural Research and Services Centre, Mashhad, Iran*

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Abstract: Alcohols and phenols were tetrahydropyranylated in the presence of $H_7[PMo_8V_4O_{40}]$ in good to excellent yields in acetonitrile and under solvent-free reaction conditions. A mild and convenient method for the formation and deprotection of ethers (THP ethers) is described. The formation of THP ethers from the corresponding alcohols was accomplished in the presence of acid-sensitive functional groups.

Keywords: tetrahydropyranyl ethers; heteropolyacid; protecting group; tetrahydropyranylation.

INTRODUCTION

Due to the easy preparation and good stability of tetrahydropyranyl groups in the presence of hydrides, alkylating agents, Grignard reagents, organometallic reagents, *etc*.,[1] they are frequently used for the protection of alcohols and phenols. In addition, they serve as stable protecting groups in peptide, nucleoside, nucleotide, carbohydrate and steroid chemistry. Tetrahydropyranylation of alcohols can be accomplished using *p*-toluenesulfonic acid (*p*-TSA),[2] $BF_3\cdot OEt_2$[3] and pyridinium ptoluenesulfonate (PPTS).[4] Recently, some developed reagents have been used for this purpose, such as $ZrCl_4$,[5] I_2,[6] LiBr,[7] acetonyltriphenylphosphonium bromide,[8] tetrabutylammonium tribromide (TBATB),[9] aluminium chloride hexahydrate,[10] indium(III) trifluoromethanesulfonate ($In(OTf)_3$),[11] alkylimidazolium tetrachloroaluminates,[12] $InCl_3$ immobilized in ionic liquids,[13] polystyrene-bound tin(IV) porphyrin,[14] Dowex 50WX4-100,[15] pyridinium chloride,[16] $SiO_2\cdot$*p*-TSA,[17] *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea and a polystyrene-bound analogue,[18] $Al(OTf)_3$,[19] and bromodimethylsulphonium bromide.[20] The employment of protective groups is an important procedure in organic synthesis.[21]

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* Corresponding author. E-mail: aligharib5@yahoo.com

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Among numerous protecting groups of alcohols, the tetrahydropyranyl (THP) group is one of the most frequently employed protecting groups due to its stability towards most non-acidic reaction conditions, ease of preparation, and facile removal under mild acidic conditions. Recent examples include stannous chloride dihydrate,[22] and heterogeneous catalysts such as sulphuric acid adsorbed on silica gel,[23] ionic liquids[24] and polyoxometalate.[25] For the deprotection of tetrahydropyranyl ethers (THP ethers), reagents including tetrafluoroborate anion,[26] sodium bromate,[27] CBr_4,[28] and montmorillonite clays[29,30] have been employed. Also, reductive reaction of tetrahydropyranyl ethers were reported in the literature.[31] Mild and chemoselective protection and deprotection of hydroxyl functionality are essential parts in the synthetic operation of polyfunctional organic compounds,[21] especially in the context of natural product and carbohydrate chemistry. Furthermore, its precursor, 3,4-dihydro-2*H*-pyran (DHP) is relatively inexpensive, rendering the process amenable to large-scale processes.[32] A heteropolyacid is an oxide cluster that has a type of phosphorus/silicon oxo acid and oxo acids with molybdenum, tungsten and other elements. The application of heteropolyacid as catalytic materials is growing continuously in the field of catalysis.[33] These compounds possess unique properties, such as: well-defined structure, Brønsted acidity, possibility to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility, *etc*.[34] Acidity, basicity, and pseudo liquid behaviour are the principal factors governing the acid catalysis by solid heteropolyacids. The acidic properties are mainly controlled by *i*) the structure and composition of the heteropoly anion itself, *ii*) the counter cations and *iii*) the dispersion on supports. The acid strength can be controlled mainly by *i*), and the number of acid sites is greatly influenced by *ii*) and *iii*). Besides, soft basicity of the heteropoly anion itself sometimes plays an important role for high catalytic activity in acid-catalyzed reactions. The acid strength of hydrogen forms in the solid state reflects on the general the acidity in solution and it decreases when W is replaced by Mo and when the central P atom is replaced by Si in Keggin heteropolyacids, whereby Keggin heteropolyacids are stronger acids than Dawson heteropolyacids.[35]

EXPERIMENTAL

Materials and methods

All chemical materials were purchased from Merck and used without further purifycation.

Instruments

The ^{1}H-NMR spectra were recorded on a FT NMR Bruker 300 MHz spectrometer at 298 K. Chemical shifts were reported in ppm (δ-scale) relative to the internal standard TMS (0.00 ppm); the solvent was used as a reference. Melting points (m.p.) were recorded on an Electrothermal type 9100 melting point apparatus and are uncorrected. The products were identified by comparison of their m.p., IR and NMR spectra with those of authentic samples.

Catalyst preparation

The catalysts $H_4[PMo_{11}VO_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_6[PMo_9V_3O_{40}]$, $H_7[PMo_8V_4O_{40}]$ and Wells–Dawson, $H_6[P_2W_{18}O_{62}]$ were prepared in accordance to literature methods.[36–41]

General procedure for the protection of alcohols using the heteropolyacid catalysts in the presence of solvents

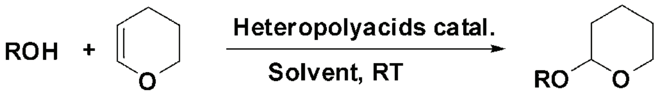
To a mixture of benzyl alcohol (1.0 mmol) and DHP (1.0 mmol) in dry CH_3CN (5 mL) was added a heteropolyacid catalyst (1.2 mol), and the resulting mixture was stirred at room temperature for the appropriate time until the complete disappearance of the starting alcohol was confirmed by thin layer chromatography (TLC). After completion of the reaction, the solid catalyst was removed by simple filtration. Evaporation of the solvent under reduced pressure gave the almost pure THP ether. Column chromatography of the filtrate on silica gel using *n*-hexane:EtOAc (6:1) as eluent gave benzyl tetrahydropyranyl ether in high yield.

General procedure for the solvent-free protection of alcohols using heteropolyacid catalysts

To a mixture of benzyl alcohol (1.0 mmol) and DHP (1.0 mmol) was added a heteropolyacid catalyst (1.2 mol), and the resulting mixture was stirred at room temperature for the appropriate time until the complete disappearance of the starting alcohol (as monitored by TLC). After completion of the reaction, reaction, $CHCl_3$ (5 ml) was added and the organic phase was obtained by simple filtration. Evaporation of the solvent under reduced pressure gave the almost pure THP ether. Column chromatography of the filtrate on silica gel using *n*-hexane:EtOAc (6:1) as eluent gave benzyl tetrahydropyranyl ether in high yield.

RESULTS AND DISCUSSION

Alcohols, phenols, 3,4-dihydro-2*H*-pyran (DHP), and $H_7[PMo_8V_4O_{40}]$ and other heteropolyacid catalysts were stirred in CH_3CN at room temperature to yield the corresponding THP ethers. The tetrahydropyranylation of alcohols and phenols in the presence of $H_7[PMo_8V_4O_{40}]$ was investigated and herein, a mild and efficient method for the conversion of alcohols to THP compounds is reported. First, the protection of benzyl alcohol in the presence of $H_7[PMo_8V_4O_{40}]$ and other heteropolyacid catalysts was studied. Benzyl tetrahydropyranyl ether was formed after appropriate times. Then, these conditions were applied for the protection of structurally different alcohols and phenols (Scheme 1).



Scheme 1. Tetrahydropyranylation of phenols and alcohols using heteropolyacid catalysts.

Various aromatic and aliphatic alcohols were tetrahydropyranylated to THP compounds using $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst in good to high yields under ambient conditions without any by-products. Employing the ratios shown in Table I, the best results were obtained and THP ethers were produced in good to excellent yields. The results of tetrahydropyranylation of alcohols to THP ethers are presented in Table I. As can be seen in Table I, primary, secondary and tertiary alcohols and phenols were all protected under the employed conditions. Thus, this method is very suitable for the protection of various types of alcohols and phenols, providing a novel application of $H_7[PMo_8V_4O_{40}]$ heteropolyacid catalyst in organic synthesis.

TABLE I. Preparation of THP ethers in the presence of $H_7[PMo_8V_4O_{40}]$ catalyst in MeCN and under solvent-free conditions (The products were characterized by their physical properties, comparison with authentic samples, and by spectroscopic methods. The reaction was performed at room temperature. Molar ratios for ROH/DHP/$H_7[PMo_8V_4O_{40}]$, (HPAs) catalysts were 1:1:1.2)

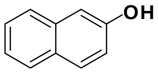
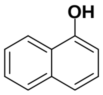
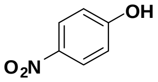
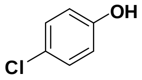
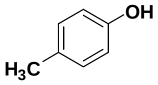
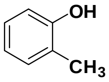
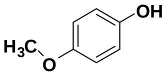
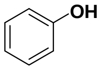
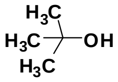
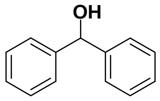
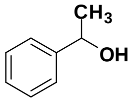
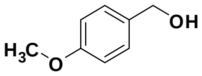
Entry	ROH	CH_3CN		Solvent-free	
		meTi, min	Isolated yield, %	Time, min	Isolated yield, %
1		32	65.5	20	69
2		33	80	23	82
3		23	91	21	80.5
4		25	95	24	93.4
5		8	96	10	94.4
6		9	90	9	90
7		10	98	8	95.5
8		9	96	10	97
9		7	89	6	88
10		15	91	16	93
11		18	98	20	99
12		8	96.3	11	98

TABLE I. Continued

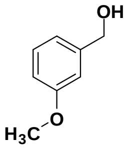
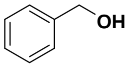
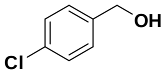
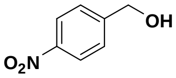
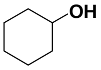
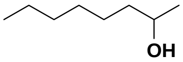
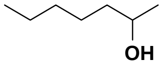
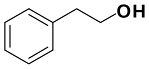
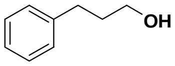
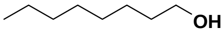
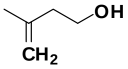
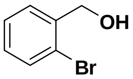
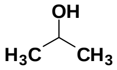
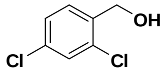
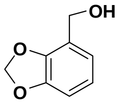
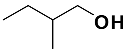
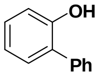
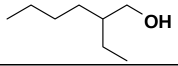
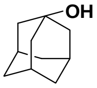
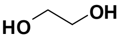
Entry	ROH	CH_3CN		Solvent-free	
		Time, min	Isolated yield, %	Time, min	Isolated yield, %
13		5	97.5	7	95
14		11	98	10	97
15		16	90.6	19	93
16		17	86	15	88
17		23	97.5	25	98
18		30	98.5	30	96
19		31	97.5	29	96
20		7	98	11	98
21		6	97	9	97
22		9	91.5	10	94
23		9.5	93.5	9	91
24		14	94.5	17	95
25		8	92	12	94
26		7	94	9	90.5
27		16	93	15	93
28		11	93.2	12	95.5
29		19.5	87	18	89.5
30		8.5	91.2	11.5	93

TABLE I. Continued

Entry	ROH	CH_3CN		Solvent-free	
		Time, min	Isolated yield, %	eTim, min	Isolated yield, %
31		27.5	94.5	29	91.6
32		21	92.4	20	90.5

This method was found to be highly selective for primary alcohols. In a binary mixture of 3-phenyl-1-propanol and 2-octanol, the primary alcohol was completely converted to corresponding THP ether, while only 8 % of 2-octanol reacted. Similarly, excellent selectivity was observed for tetrahydropyranylation of benzyl alcohol in the presence of 1-phenylethanol (Table II, entry 2). Primary and secondary alcohols were selectively converted to THP ethers in the presence of a tertiary alcohol (Table II, entries 5 and 6). Furthermore, this method showed excellent selectivity in the tetrahydropyranylation of alcohols in the presence of phenols (Table II, entry 7).

TABLE II. Selectivity of the reactions of different binary mixtures with DHP/$H_7[PMo_8V_4O_{40}]$

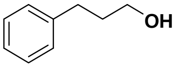
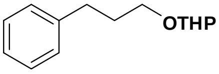
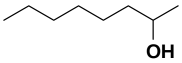
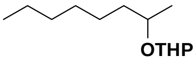
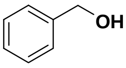
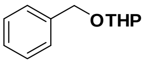
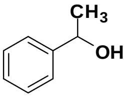
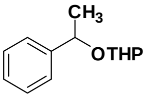
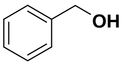
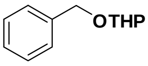
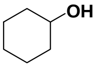
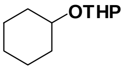
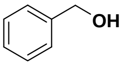
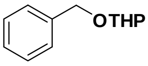
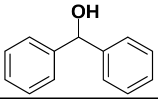
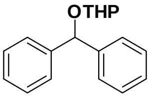
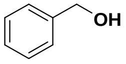
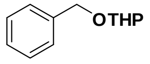
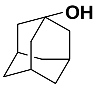
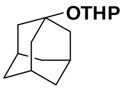
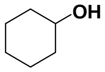
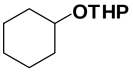
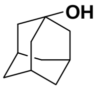
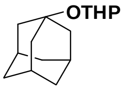
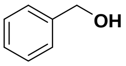
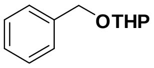
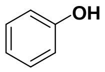
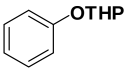
Entry	Binary mixture	Product	Time, min	Yield[a], %
1			11	91.5
				8
2			18	93.2
				6
3			22	83
				16
4			14	100
				0

TABLE II. Continued

Entry	Binary mixture	Product	Time, min	Yield[a], %
5			23	91
				9
6			21	82
				18
7			18	92
				8

[a] GC yield using internal standard; ROH:DHP:$H_7[PMo_8V_4O_{40}]$ = 1:1:1.2; the reaction was performed at room temperature

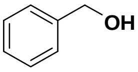
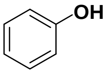
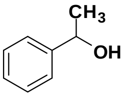
Effect of the catalyst type

In order to compare the kinds of vanadium(V)-substituted polyoxomolybdates, *i.e.*, $H_4[PMo_{11}VO_{40}]$, $H_5[PMo_{10}V_2O_{40}]$, $H_6[PMo_9V_3O_{40}]$, and Wells–Dawson catalysts, with the $H_7[PMo_8V_4O_{40}]$ catalyst in the tetrahydropyranylation of alcohols and phenols, these catalysts were used for the tetrahydropyranylation of alcohols and phenols. The results are shown in Table III. The yield of product decreased in the following order: $H_7[PMo_8V_4O_{40}] > H_6[P_2W_{18}O_{62}] > H_6[PMo_9V_3O_{40}] > H_5[PMo_{10}V_2O_{40}] > H_4[PMo_{11}VO_{40}]$. The results showed that $H_7[PMo_8V_4O_{40}]$ was the most efficient catalyst for THP with a higher activity than the Keggin and Dawson heteropolyacids. The larger number of protons in its structure may lower the activation barrier for the alkylation reaction. In addition, the large anion also provides many "sites" on the molecule that are likely to contribute to the effectiveness of the catalyst. Comparison of the results obtained using vanadium (V)-substituted polyoxomolybdates types of heteropolyacids and Wells–Dawson catalysts with those reported for $H_7[PMo_8V_4O_{40}]$ and Dawson type catalysts shows some advantages of the former catalysts in these reactions (Table III).

Spectroscopic data for the new compound ***16***

Compound ***16*** *(Table I)*. Yellowish oil (eluted with *n*-hexane: EtOAc, 6:1). ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 1.48–1.90 (6H, *m*), 3.52 (1H, *m*), 3.89 (1H, *m*), 4.42 (1H, *d*, J = 11.6 Hz), 4.70 (1H, *m*), 4.80 (1H, *d*, J = 12.0 Hz), 7.25 (4H, *m*); ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 147.6, 146.6, 128.1, 123.9, 98.7, 68.0, 62.6, 30.8, 25.7, 19.6; HRMS (EI): Calcd. for $C_{12}H_{15}O_4N$ $[M]^+$, 237.1001. Found: 237.1003.

TABLE III. The role of the heteropolyacid on the tetrahydropyranylation under solvent-free reaction conditions

Entry	Substrate	Catalyst	Time, min	Yield[a], %
1		$H_7[PMo_8V_4O_{40}]$	10	97.3
2	A	$H_6[P_2W_{18}O_{62}]$	10	94.5
3	A	$H_6[PMo_9V_3O_{40}]$	10	92.2
4	A	$H_5[PMo_{10}V_2O_{40}]$	10	91.5
5	A	$H_4[PMo_{11}VO_{40}]$	10	88.6
6		$H_7[PMo_8V_4O_{40}]$	10	97
7	B	$H_6[P_2W_{18}O_{62}]$	10	94
8	B	$H_6[PMo_9V_3O_{40}]$	10	91.5
9	B	$H_5[PMo_{10}V_2O_{40}]$	10	90
10	B	$H_4[PMo_{11}VO_{40}]$	10	88.5
11		$H_7[PMo_8V_4O_{40}]$	22	99
12	C	$H_6[P_2W_{18}O_{62}]$	22	96.5
13	C	$H_6[PMo_9V_3O_{40}]$	22	94.3
14	C	$H_5[PMo_{10}V_2O_{40}]$	22	91.5
15	C	$H_4[PMo_{11}VO_{40}]$	22	90.4

[a]Isolated yield determined by GC. The reaction was performed at room temperature. Substrate of entry **1**: compound A, substrate of entry **6**: compound B and substrate of entry **11**: compound C

CONCLUSIONS

In summary, a novel method using different vanadium(V)-substituted polyoxomolybdates and Wells–Dawson heteropolyacids as inexpensive, non-corrosive and environmentally benign catalysts for protection of phenols and alcohols as THP ethers was developed. The advantages of the presented procedure are simplicity of operation and work-up and good yields of products, mild conditions, short reaction times and high yields (> 90 %).

ИЗВОД

КАТАЛИТИЧКА ТЕТРАХИДРОПИРАНИЛАЦИЈА ФЕНОЛА И АЛКОХОЛА ВАНАДИЈУМ(V)-СУПСТИТУИСАНИМ ПОЛИОКСОМОЛИБДАТИМА

ALI GHARIB[1,2] и MANOUCHEHR JAHANGIR[1]

[1]*Department of Chemistry, Islamic Azad University, Mashhad* и [2]*Agricultural Research and Services Center, Mashhad, Iran*

Успешно је извршена реакција алкохола и фенола са тетрахидропираном у присуству $H_7[PMo_8V_4O_{40}]$ у добром до одличном приносу, без присустног растварача. Описани су благи реакциони услови за формирање и депротекцију тетрахидропиранил етара (THP етри). Грађење THP етара са одговарајућим алкохолима извршено је у присуству функционалних група које су осетљиве на киселе реакционе услове.

(Примљено 7. маја, ревидирано 9. јула 2011)

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