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Acetylation of Alcohols Catalyzed by Dodeca-tungsto(molybdo)phosphoric acid

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Summary. Acetylation of primary, secondary, and tertiary alcohols was carried out in some refluxing alkyl acetates and in two carboxylic acids with the participation of catalytic amounts of $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$, and $H_{14}P_5W_{30}O_{110}$ with good yields and high stereo(regio)specificity under mild reaction condition. $H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ have also shown excellent reactivity in the formylation of 1-butanol with ethyl formate at room temperature and in short reaction times. Heteropolyacid catalysts could be separated after a simple work up and reused for several times.

Keywords. Acetylation; Formylation; Heteropolyacid; Catalytic; Alcohol.

Introduction

The acetylation of hydroxyl groups is one of the most frequently used transformations in organic chemistry for the synthesis of valuable industrial and pharmaceutical compounds, especially in the construction of polyfunctional molecules such as nucleosides, carbohydrates, steroids, and natural products [1]. Therefore the protection of this functional group is of prime importance while carrying out reactions sensitive to such functionality in a multifunctional substrate [1–3]. Among the various protecting groups used for the hydroxyl function, acetyl is the most common group in view of its easy introduction, being stable to the acidic reaction conditions, and also easily removable by mild alkaline hydrolysis [4–6]. Acetyl chloride and acetic anhydride are generally used as acetylating agents in the presence of tributylphosphine or pyridine derivatives [7–9]. Lewis acid catalysts such as $Sc(OTf)_3$ [9], *TMS*O*Tf* [10], $Cu(OTf)_2$ [11], $TaCl_4$ [12], $In(OTf)_3$ [13], $CoCl_2$ [14], and yttria-zirconia based *Lewis* acids have also been reported to be efficient catalysts for acetylation of alcohols [15].

Homogeneous catalysis with using heteropolyoxometalates has been widely developed in a broad range of organic synthesis and environmentally benign catalysis

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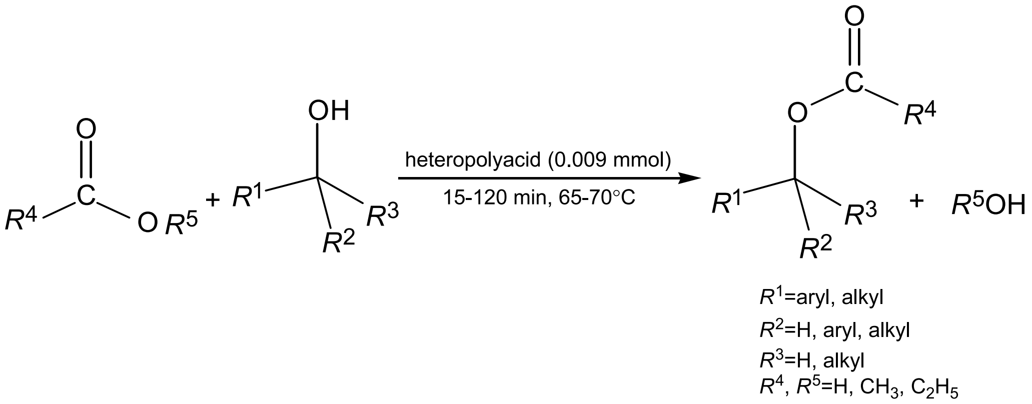

Scheme 1

during the past few decades. Good yields, high selectivity, economically convenience, ease of work up, high stability and high catalytic activity of heteropolyacids have motivated increasing potential for homogeneous catalysis in organic synthesis, biomedical transformations, and environmentally benign catalysis [16–18]. *Keggin*-type heteropolyacids with the general formula of $H_{8-x}[XM_{12}O_{40}]$, where *X*, *x,* and *M* are, respectively, the hetero-atom (*e.g.* P^{5+} or Si^{4+}), its oxidation state, and the addenda atom (usually Mo^{6+} or W^{6+}), are the most common for industrial catalysis such as oxidation of olefins, alkanes, alcohols, amines, and bond-breaking of Sn–C [19–26].

Now, we wish to introduce the results of acetylation of some primary, secondary, and tertiary alcohols with some alkyl acetates under reflux conditions catalyzed by some *Keggin*-type heteropolyacids (Scheme 1). Since heteropolyacids are harmless to the environment with respect to corrosiveness, safety, quantity of waste, and separability, they are promising solid acid catalysts to replace environmentally harmful liquid acid catalysts such as H_2SO_4 and other conventional solid acids such as $SiO_2–Al_2O_3$, $H_3PO_4–SiO_2$, and zeolites [27–29].

Results and Discussion

Acetylation of some alcohols was studied in refluxing ethyl acetate mediated by catalytic amounts of different acidic and anionic heteropolyoxometalates under mild reaction conditions (Table 1) [30]. In a control experiment without any catalyst, no acetylation was observed over the same or prolonged reaction time. Meanwhile, phenols, thiols, and aromatic amines are unaffected under these reaction conditions. Among the inspected catalysts, Mo-based heteropolyacid, $H_3PMo_{12}O_{40,}$ was the most efficacious catalyst in the acetylation of 1-butanol and led to 92% of **1b** within 2 h. Whereas, 85% of 1-butyl acetate was obtained in the presence of $H_3PW_{12}O_{40}$ at the same time. The *Preyssler* $H_{14}P_5W_{30}O_{110}$ has also revealed good catalytic activity in the acetylation of 1-butanol. It provided 79% of 1-butyl acetate after 2 h. Although $H_3PMo_{12}O_{40}$ was a potent catalyst in the acetylation of **1a**, its tetra-*n*-butyl ammonium salt, $(TBA)_3PMo_{12}O_{40}$, was almost inactive. Other W- and Mo-based catalysts, such as $Na_6P_2Mo_{18}O_{62}$, $K_6P_2W_{18}O_{62}$, $(TBA)_7PW_{11}O_{39}$, and $Na_3PW_9Mo_3O_{40}$ have revealed the least catalytic activity in the acetylation of 1-butanol.

Table 1. Acetylation of alcohols with ethyl acetate catalyzed by some heteropolyacids[a]

Substrate	Catalyst	Time/h	Product	Yield/%
$H_3C(CH_2)_3OH$ (**1a**)	$H_3PW_{12}O_{40}$	2	$H_3C(CH_2)_3OAc$ (**1b**)	85
1a	$H_3PMo_{12}O_{40}$	2	**1b**	92
1a	$H_{14}P_5W_{30}O_{110}$	2	**1b**	79
$H_3C(CH_2)_2OH$ (**1c**)	$H_3PMo_{12}O_{40}$	2	$H_3C(CH_2)_2OAc$ (**1d**)	77
$H_3C(CH_2)_5OH$ (**1e**)	$H_3PMo_{12}O_{40}$	2	$H_3C(CH_2)_5OAc$ (**1f**)	80
$H_3C(CH_2)_6OH$ (**1g**)	$H_3PMo_{12}O_{40}$	2	$H_3C(CH_2)_6OAc$ (**1h**)	83
1g	$Na_3PW_{12}O_{40}$	2	**1h**	30
$C_6H_5CH_2OH$ (**1i**)	$H_{14}P_5W_{30}O_{110}$	2	$C_6H_5CH_2OAc$ (**1j**)	68
1i	$H_3PW_{12}O_{40}$	2	**1j**	34
1i	$H_3PMo_{12}O_{40}$	2	**1j**	7
$3\text{-}NO_2\text{–}C_6H_4CH_2OH$	$H_3PMo_{12}O_{40}$	2	$3\text{-}NO_2\text{–}C_6H_4CH_2OAc$	39
$4\text{-}Cl\text{–}C_6H_4CH_2OH$	$H_3PMo_{12}O_{40}$	2	$4\text{-}Cl\text{–}C_6H_4CH_2OAc$	45
$4\text{-}NO_2\text{–}C_6H_4CH_2OH$	$H_3PMo_{12}O_{40}$	2	$4\text{-}NO_2\text{–}C_6H_4CH_2OAc$	33
$(CH_3)_3COH$ (**1k**)	$H_3PMo_{12}O_{40}$	1	$(CH_3)_3COAc$ (**1l**)	46
1k	$H_{14}P_5W_{30}O_{110}$	1	**1l**	60
1k	$H_3PW_{12}O_{40}$	1	**1l**	62
1k	$Na_3PW_{12}O_{40}$	1	**1l**	41
Adamantanol	$H_3PMo_{12}O_{40}$	1	Adamantanyl acetate	52
$(CH_3)_2CHOH$ (**1m**)	$H_3PMo_{12}O_{40}$	2	$(CH_3)_2CHOAc$ (**1n**)	17
1m	$Na_3PW_{12}O_{40}$	6	**1n**	11
1m	$H_3PW_{12}O_{40}$	2	**1n**	24
(−)-Menthol	$H_3PMo_{12}O_{40}$	2	(−)-Menthyl acetate	26
Cyclohexanol (**1o**)	$H_3PW_{12}O_{40}$	6	Cyclohexyl acetate (**1p**)	55
1o	$H_3PMo_{12}O_{40}$	6	**1p**	55
$SH(CH_2)_4OH$ (**1q**)	$H_3PMo_{12}O_{40}$	2	$SH(CH_2)_4OAc$ (**1r**)	65
$4\text{-}OH\text{–}C_6H_4(CH_2)_2OH$ (**1s**)	$H_3PMo_{12}O_{40}$	2	$4\text{-}OH\text{–}C_6H_4(CH_2)_2OAc$ (**1t**)	75
$C_6H_5NH_2$	$H_3PMo_{12}O_{40}$	6	C_6H_5NHOAc	0
C_6H_5OH	$H_3PMo_{12}O_{40}$	6	C_6H_5OAc	0

[a] Alcohol (2 mmol) was added to a solution of heteropolyacid (0.009 mmol) in ethyl acetate (4 cm^3, 40 mmol) and the reaction mixture was allowed to stir at 65–70°C for the required time; mol ratio of catalyst:alcohol:ethyl acetate was 1:222:4444; progress of the reaction was followed by withdrawing aliquots directly from the reaction mixture for GLC or TLC analysis; isolated yields were based on the starting materials; all products were characterized by comparison of their spectral and physical data with those of known samples

In order to extend the scope of this acetylation method, some linear, secondary, and tertiary alcohols were exposed to the acetylation reactions catalyzed by dodeca-tungsto(molybdo)phosphoricacids in refluxing ethyl acetate. In the acetylation of linear alcohols, 1-propanol (**1c**), 1-butanol (**1a**), 1-hexanol (**1e**), and 1-heptanol (**1g**) were examined; among them 1-butanol has led to the highest yield. The *Preyssler* $H_{14}P_5W_{30}O_{110}$ and *Keggin* $H_3PMo_{12}O_{40}$ behaved alike in the acetylation of benzyl alcohol (**1i**), whereas $H_3PW_{12}O_{40}$ was obviously less effective than the two above mentioned catalysts. These three catalysts have provided benzyl acetate (**1j**) with 68, 70 and 34% yields, respectively, under the same reaction conditions after 2 h. ^{t}Butanol (**1k**) and 1-adamantanol, as tertiary alcohols, have resulted in 46 and 52% of their corresponding acetates, respectively, catalyzed by

$H_3PMo_{12}O_{40}$ after 1 h [31]. Isopropanol (**1m**) led to 17% of **1n** with the mediation of $H_3PMo_{12}O_{40}$ after 2 h. Whereas cyclohexanol (**1o**) produced 55% of **1p** with the two above mentioned catalysts after 6 h. Cyclohexanol and isopropanol were obviously less reactive than the other alcohols in the acetylation system. They have provided <30% yields with $H_3PMo_{12}O_{40}$ and $H_3PW_{12}O_{40}$ after 3 h. To explore stereoselectivity and regioselectivity of the acetylation method, catalytic acetylations of (−)-menthol, 2-mercaptoethanol (**1q**), and (ρ-hydroxyphenylethanol (**1s**) were examined in ethyl acetate in the presence of $H_3PMo_{12}O_{40}$. (−)-Menthol afforded 26% of (−)-menthyl acetate; whereas **1q** and **1s** led to acetylation of only the hydroxyl groups with 65 and 75% yields, respectively. Therefore, thiol and phenol groups of **1q** and **1s** were unaffected under these reaction conditions. These findings have confirmed stereo(regio)specificity of this acetylation procedure among other present and useful methodologies.

To explore effects of phenyl substituents on the acetylation of benzyl alcohols, ρ-chloro- and ρ-nitrobenzyl alcohols were exposed to the acetylation reactions with ethyl acetate catalyzed by $H_3PMo_{12}O_{40}$. Results have shown that chloro- and nitro-substituents reduce efficacy of the acetylation. ρ-Chloro- and ρ-nitrobenzyl alcohols were converted to their corresponding acetates with 45 and 33% yields, respectively, after 2 h. Whereas 70% yield was obtained with benzyl alcohol. Noteworthy, chloro- and nitro-groups were unaffected under these reaction conditions. Eventually, different reactivity patterns in the acetylation reactions may partly be explained considering acid strength of catalyst and oxidation potential of the metal center in catalyst.

Esterification of alcohols with carboxylic acids is among the fundamental and routinely used functional transformations in organic chemistry. Traditionally, it is performed using mineral or sulfonic acids as catalysts in the presence of excess of either the alcohol or carboxylic acid to shift the equilibrium to the product side.

Table 2. Acylation of 1-butanol with some acylating agents catalyzed by heteropolyacids[a]

Acetylating agent	Catalyst	Time/h	Yield/%
Ethyl acetate (**2a**)	$H_3PMo_{12}O_{40}$	2	90[b]
Acetic acid (**2b**)	$H_3PMo_{12}O_{40}$	1	100[b]
Propionic acid (**2c**)	$H_3PMo_{12}O_{40}$	1	20[d]
Ethyl formate (**2d**)	$H_3PMo_{12}O_{40}$	15 min (rt)	95[c]
2d	$H_3PW_{12}O_{40}$	5 min (reflux)	95[c]
2d	$H_3PW_{12}O_{40}$	15 min (rt)	91[c]
Methyl acetate (**2e**)	$H_3PW_{12}O_{40}$	2	87[b]
2e	$H_3PMo_{12}O_{40}$	2	85[b]
2e	$H_{14}P_5W_{30}O_{110}$	1	43[b]
Phenyl acetate	$H_3PMo_{12}O_{40}$	2	75[b]

[a] *n*-Butanol (0.18 cm^3, 2 mmol) was added to a solution of heteropolyacid (0.009 mmol) in acylating agent (40 mmol) and the reaction mixture was allowed to stir at 65–70°C for the required time; mol ratio of catalyst:alcohol:acetylating agent was 1:222:4444; progress of the reaction was followed by withdrawing aliquots directly from the reaction mixture for GLC or TLC analysis; isolated yields were based on the starting materials; [b]*n*-butyl acetate was formed; [c]*n*-butyl formate was produced; [d]*n*-butyl propionate was formed

The use of strong mineral acids, however, leads to waste streams posing environmental problems for industrial processes. It is found that our catalytic system is capable of efficient acetylation in carboxylic acids as in alkyl acetates. According to the data in Table 2, acetic acid (**2b**) was more reactive than ethyl acetate (**2a**) in the acylation of 1-butanol in the presence of $H_3PMo_{12}O_{40}$. However, 2-chloropropionic acid (**2c**) was clearly less reactive than ethyl acetate. The former produced complete conversion after 1 h, whereas the substituted propionic acid led to 20% yield at the same time.

Formylation is also an important transformation in organic synthesis. Although various formylating reagents have been reported, there are still serious limitations for the preparation of formates because of drastic reaction conditions, using uncommon reagents, and formation of undesirable or toxic by-products [32–34]. Instability of the anhydride and acid chloride of formic acid led us to examine formylation of 1-butanol by ethyl formate in this catalytic system. The results introduced in Table 2 have demonstrated effective formylation of 1-butanol with ethyl formate (**2d**). Formylation of 1-butanol could be driven to completion (>90% yield) within 15 min.

In conclusion, an eco-friendly, clean, and cheap catalytic acetylation method under mild reaction conditions using the simplest heteropolyacids has been developed for acetylation of a variety of primary, secondary, and tertiary alcohols in good yields. Simple procedure, easy work up, regenerable catalyst, and high stereo(regio)specificity, are other advantages of the acetylation method introduced here.

Experimental

Materials and Instrumentation

Alkyl acetates, alcohols, and other solvents were commercially available, and their purity was monitored by gas chromatography. All products were characterized by comparing their spectral and physical data with those of known samples. Purity of the substances and progress of the reactions were monitored by TLC on silica gel or by gas chromatography. GLC analyses were performed on a Shimadzu GC-17A instrument equipped with a flame ionization detector using 25 m × 0.25 mm CPB(5–20) capillary columns. $H_3PW_{12}O_{40}$ and $H_3PMo_{12}O_{40}$ were prepared according to the literature [35, 36] or were purchased commercially. The heteropolyoxometalates $Na_3PW_{12}O_{40}$ and $H_{14}[P_5W_{30}O_{110}]$ were prepared and characterized according to literature procedures as follows [37–39].

Synthesis of $Na_3PW_{12}O_{40} \cdot 7H_2O$

$Na_2WO_4 \cdot 2H_2O$ (10 g, 30 mmol) was slowly added to 20 cm^3 distilled water and the mixture was warmed to 60°C with stirring. Then, H_3PO_4 85% (1 cm^3, 15 mmol,) and HCl (8 cm^3, 100 mmol) were added and the resulting mixture was stirred for 1 h. The white afforded precipitate was washed with water and was recrystallized twice from hot water.

Preparation of Preyssler's Anion $K_{12.5}Na_{1.5}[NaP_5W_{30}O_{110}]$ *and it's acidic form,* $H_{14}[P_5W_{30}O_{110}]$

The potassium salt was prepared following *Alizadeh*'s method [39], or a slight variation thereof. ortho-Phosphoric acid 90% (75 cm^3, 1.2 mol) was slowly added to 50 cm^3 aqueous solution of $Na_2WO_4 \cdot 2H_2O$ (99 g, 0.3 mol) at 45°C and the resulting mixture was refluxed for 5 h. Then, the obtained solution was diluted by 15 cm^3 water. Thereafter, powdered KCl (22.5 g, 0.32 mol) was slowly added to the vigorously stirred above solution during 35 min at rt. The pale green impure precipitate was filtered off and was washed with CH_3COOK (0.1 *M*). The white needle-like crystals of potassium salt of the *Preyssler*'s anion were recrystallized from hot water.

The free acid was prepared by passage of a solution of 11.4 g potassium salt in 20 cm^3 water through a column (50×1 cm) of Dowex 50WX8 in the H^+ form. Evaporation of the elute to dryness in vacuum resulted in $H_{14}[P_5W_{30}O_{110}]$.

General Procedure for Acetylation of 1-Butanol with Ethyl Acetate Catalyzed by $H_3PMo_{12}O_{40}$

To a stirred solution of $H_3PMo_{12}O_{40}$ (0.03 g, 0.009 mmol) in ethyl acetate (4 cm^3, 40 mmol), was added 1-butanol (0.18 cm^3, 2 mmol) and the reaction mixture was allowed to stir at 65–70°C for the required time. Progress of the reaction was followed by aliquots withdrawn directly from the reaction mixture, analyzed by gas chromatography using internal standard or by TLC using ethyl acetate hexane (1/5) mixture as eluent. After completion of the reaction, ethyl acetate was removed under reduced pressure and ether was added. Evaporation of the organic solution was followed by column chromatography on a short pad of silica gel using petroleum ether as eluent to afford 1-butyl acetate as a liquid. The residue on silica gel was washed with a mixture of water ethanol (1/1) to dissolve the catalyst. Thereafter, the catalyst could be separated and reused several times after vacuum drying. However, the catalyst activity was gradually declining in successive runs. The yield of 1-butyl acetate produced from the reaction of 1-butanol with ethyl acetate promoted by the recovered $H_3PMo_{12}O_{40}$ for three times remained 90–92% and after six times was 75–78% under the reaction conditions described here.

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