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A Simple and Mild Acylation of Alcohols, Phenols, Amines, and Thiols with a Reusable Heteropoly Acid Catalyst ($H_6P_2W_{18}O_{62} \cdot 24 H_2O$)

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Abstract: The acylation of alcohols, phenols, thiols, and amines with varied substitution using acid anhydrides is efficiently catalyzed by Wells-Dawson heteropoly acid ($H_6P_2W_{18}O_{62} \cdot 24 H_2O$). Reactions proceed with very good to excellent yield in air at room temperature, using toluene as solvent (40 examples). The bulk catalyst was easily reused without appreciable loss of its activity.

Keywords: Acylation; Alcohols; Amines; Heteropolyacid; Phenols; Thiols; Wells-Dawson catalyst.

Introduction

Hydroxyl and amino groups are widely occurring functional groups in molecules in nature, and they can also be found in a number of compounds of biological and synthetic significance¹ including flavonoids, steroids, carbohydrates, amino acids, nucleosides, *etc.* Protection of alcoholic and phenolic hydroxyl groups is currently required, acetylation being one of the most general reactions. Different procedures can be applied², involving an acid chloride or acid anhydride with a base³⁻⁶, or an acid anhydride in the presence of an acid catalyst. Homogeneous catalysts currently used for this purpose are *p*-toluenesulfonic acid and sulfamic acid^{7a}, and a variety of Lewis acids including simple salts^{7a-g} and various triflates^{7a, c, h}. Besides, iodine^{7a}, NBS^{8a}, Sc (NTf₂)^{3,8b} acetylimidazole^{8c}, and PPh₃/CBr₄^{8d} have been employed as catalysts for achieving alcohol acetylation and formylation.

Amines and thiols are acylated using Lewis acids as catalysts, for example LiCl,^{7d} Mg(ClO₄)₂,^{7e} or InCl₃.^{7g} In spite of their efficiency, the above mentioned soluble catalysts have some disadvantages: industrial use of mineral acids leads to serious environmental problems due to highly acidic waste streams; Lewis acids are efficient as catalysts but most of them are wasteful because they are usually hydrolyzed during the isolation, and triflates are generally expensive.

In recent years there has been great interest in the reactions performed under heterogeneous catalysis, because of the possibility of recovering and recycling the acid catalyst, largely reducing the environmental impact. A diversity of noncorrosive materials have been used as heterogeneous catalysts. Some of them are zeolite HSZ-360^{9a} and zirconium sulfophenyl phosphonate^{9b}, used for acetylating alcohols/phenols. Nafion-H^{9c} is useful for acetylating alcohols, amines and thiols, while alcohol acetylation/formylation can be achieved by using the heteropolyacid and the corresponding salt^{9d,e,f}. In general, the reactions have proved to be simpler and cleaner.

Heteropolyacids are constituted by a close-packed framework of metal-oxygen octahedra MO₆ (M=Mo⁶⁺, W⁶⁺) surrounding a central atom X (Si⁴⁺, P⁵⁺). Wells-Dawson (WD) catalyst^{11,12} exhibits superacidic properties, and can be used in bulk or supported form in reactions requiring electrophilic catalysis. We have employed WD acid for performing aldehyde^{13a} and other alcohol/phenol^{13b} protection and deprotection and, more recently, for catalyzing the Pechmann reaction^{13c}.

In the present letter we report a catalytic procedure for easily acylating a variety of primary and secondary alcohols, phenols, amines, and thiols with Ac₂O at room temperature in toluene. This procedure can also be used for preparing phenyl and alkyl esters from other acid anhydrides, under heterogeneous catalysis by bulk WD acid.

Experimental

General Procedures

Commercially available alcohols, phenols, thiols, and amines, Aldrich or Fluka, were distilled or recrystallized before use. ¹H-RMN spectra (CDCl₃) were recorded on Bruker 200 MHz spectrometer using TMS as internal standard. Low-resolution mass spectra were recorded on a Perkin Elmer GC-MS model (Q-MASS 910). Spectral data agree with the expected values. The purity determination of most of the products was accomplished by GC analysis on a Perkin Elmer instrument and TLC on silica gel 60 F254 plates, for co-injection with authentic samples prepared by known methods. The purity established by GLC was better than 97% in all the cases.

The Dawson acid (H₆P₂W₁₈O₆₂·24H₂O) was prepared by the Drechsel method from a α/β K₆P₂W₁₈O₆₂·10H₂O isomer mixture. This Dawson-type salt was prepared according to the technique reported by Lyon *et al*.¹¹. Concentrated H₃PO₄ in a 4:1 acid/salt ratio was added to a boiling aqueous solution of Na₂WO₄·2H₂O, and the mixture was kept boiling in a reflux system for 8h. The salt was precipitated by adding KCl, then purified by recrystallization and cooled overnight to 278 K. The product, which is a mixture of the α and β isomers, was filtered, washed and then vacuum-dried for 8 h.

The acid¹² was obtained from an aqueous solution of α/β K₆P₂W₁₈O₆₂·10H₂O salt, which was treated with ether and concentrated HCl (37%) solution. The Dawson acid so released formed an addition compound with the ether, which allows it to be separated from the solution. After obtaining the ether solution with the acid, the ether was eliminated by flowing dry air and the remaining solution was placed in a vacuum desiccator until crystallization.

General procedure for the acylation of alcohols, phenols, amines, and thiols

A mixture of alcohol, phenol, amine or thiol (1 mmol), toluene (1 mL), acetic anhydride (1.5 mmol) and WD catalyst (1 mmol %, *ca.* 44 mg) was stirred at room temperature for the stated time (Tables 1-4). The catalyst was removed by filtration and was then washed with toluene (1 mL). The solution was concentrated and the residue was generally subjected to column chromatography on silica to give the desired alkyl acetates, aryl carboxylates, amides or thiol esters.

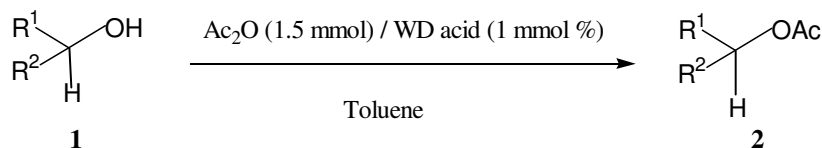
All the products were identified by comparison of analytical data (TLC, mp, IR, NMR) with those reported or with authentic samples prepared by the conventional method.

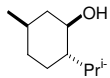

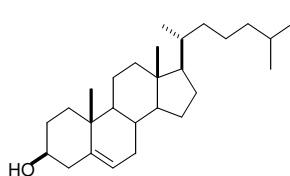
Results and Discussion

Reaction conditions were optimized varying temperature, anhydride:substrate and WD-acid:substrate ratios, the amount of catalyst, and the reaction time. Experiments for checking the reutilization of the catalyst showed almost no decrease in yields over three successive batches. In these experiments the catalyst was washed with toluene and was then reused in subsequent reactions.

Acetylation of alcohols

Primary alcohols (Table 1) acetylate with better yields (entries 1, 2 and 5) than secondary alcohols (for example, entries 3 and 8) showing the importance of the steric factor. The best yield of 1-decyl acetate was attained at *ca.* 1 h of reaction at room temperature. Shorter and longer times gave somewhat lower yields. Besides, using 5% catalyst and keeping other reaction conditions unchanged, or when a double amount of Ac₂O was used, yields were 1-2% higher than the values recorded in Table 1.

**Table 1.** WD-Acetylation of alcohols with Ac₂O

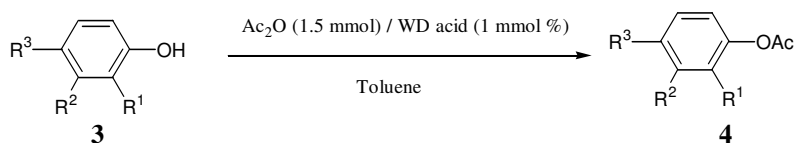
Entry	R ¹	R ²	Reaction time, h	Yield of 2, %
1	<i>n</i> -C ₉ H ₁₉	H	1	96
2	PhCH ₂ CH ₂	H	1	99
3	PhCH ₂ CH ₂	<i>n</i> -C ₃ H ₇	1	93
4	PhCH ₂	Me	1	93
5	Ph	H	0.75	98 ^a
6	Ph	Ph	1	97
7			1	93
8			1	85 ^b

^aYields of isolated product over three subsequent batches were 97, 96, and 96 %, respectively.

^b For each mmol of cholesterol, 2 mL of toluene were used.

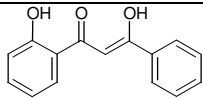
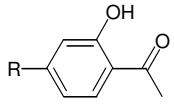
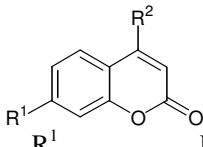
Acetylation of phenols

Phenols **3** gave their acetates in very good to excellent yields (Table 2). Different reaction times are required according to the nature of their substituents (see for example, entries 3, 4, 6, 8); *o*-nitrophenol requires a higher reaction time, as well as a higher catalyst: substrate ratio, than the other examples. The intramolecular H-bond in *o*-hydroxyacetophenones was overcome, as is demonstrated by the good yields obtained (entries 17 and 18), although another similar H-bond was not (entry 16). *Ortho*-substituted phenols acetylate with good yields, the lower of them was obtained for the diacetylation of catechol (entry 5). The enol function in 4-hydroxycoumarin was selectively acetylated in good yield (entry 19) in a homogeneous process using acetone as solvent, because these coumarins are insoluble in toluene at room temperature. However, another example bearing vinyl OH (the yellow tautomer of *o*-hydroxybenzoyl benzoyl methane, entry 16) does not undergo acetylation, but a slow cyclization to flavone yielding 8 % by continued stirring at room temperature. Experiments for recovering and recycling the catalyst were performed using phenol as the substrate, the reaction conditions being as defined above.

**Table 2.** WD-Acetylation of phenols with Ac₂O

Entry	R ¹	R ²	R ³	Reaction time, h	Yield of 4, %
1	H	H	H	1	96 ^a
2	Me	H	H	0.75	95
3	OMe	H	H	0.5	95
4	NO ₂	H	H	5	93 ^b
5	OH	H	H	3	87 ^c
6	H	Br	H	1	99
7	H	F	H	2	94
8	H	NO ₂	H	3	90
9	H	H	Cl	1	98
10	H	H	Me	0.75	98
11	H	H	OMe	0.5	92
12	H	H	Ph	1	95
13				1	93
14				2	90
15				0.5	98

Contd...

16		10	---	^d	
17		R	H	3	95
18		R	Br	3	88
19		R ¹	R ²	2	87 ^c
20		R ¹	R ²	2	91

^aYields of isolated product over three subsequent batches were 95, 94, and 94 %, respectively.

^bA ratio 5 : 1 (Ac₂O : phenol) was used. ^cYield of the diacetate. ^dFlavone was isolated, see text.

^eC-acylation was not observed. Solvent was acetone (2 mL, see text).

Acetylation of thiols and amines: Acylation using other anhydrides

Aromatic and aliphatic representative thiols were tested for their acetylation. In both cases the reaction is complete in about 1 h at room temperature, no progress was observed by extending the reaction time. Besides, some aromatic amines were tested for the reaction, requiring lower reaction time than phenol or thiophenol to obtain very good yields of the corresponding amides (Table 3).

Table 3. WD-Acylation of amines and thiols with Ac₂O

Compound	Reaction time, h	Yield of amides and thiol esters, %
PhNH ₂	0.25	98
<i>p</i> -ClC ₆ H ₄ NH ₂	0.25	95
<i>p</i> -MeC ₆ H ₄ NH ₂	0.25	96
<i>n</i> -C ₁₆ H ₃₃ SH	1	92 ^a
PhSH	1	98 ^a

^aYields were expressed from GLC data.

Table 4. WD-Acylation of phenol and benzyl alcohol with acid anhydrides^a

Acid anhydride	% Yield of phenyl ester	% Yield of benzyl ester
(MeCO) ₂ O	96 ^b	98 ^b
(ClCH ₂ CO) ₂ O	93	96
(C ₂ H ₅ CO) ₂ O	94	97
(<i>n</i> -C ₃ H ₇ CO) ₂ O	90	92
(PhCO) ₂ O	96	94

^a Reaction time: 1 h (PhOH) or 0.75 h (PhCH₂OH); 20°C temperature.

^b Results included for comparison purposes (Tables 1 & 2).

Furthermore, different both aliphatic and aromatic acid anhydrides were also used for performing the catalytic WD-acylation of phenol and benzyl alcohol as the selected substrates (Table 4). Reaction conditions were those of the acetylation of phenol and benzyl alcohol, respectively.

Conclusions

The procedure described above provides a useful alternative for the acetylation of alcohols, phenols, amines, and thiols in mild conditions. It is general, rapid, selective, inexpensive, and environmentally friendly. The use of Wells-Dawson heteropolyacid allows the acetylation to occur efficiently, with very good to excellent yields and high purity of the products, these advantages being especially valuable for industrial applications. Studies are in progress in our laboratories in relation to the use of supported catalysts.

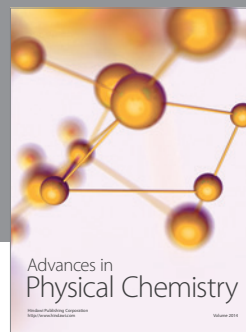
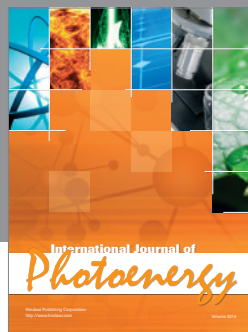
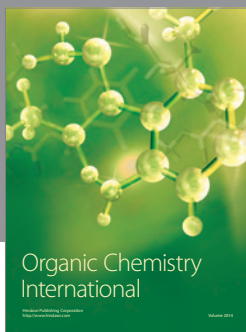
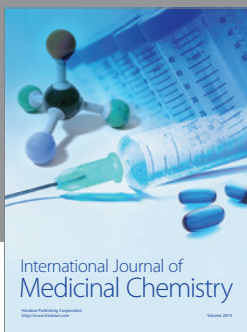
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