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Efficient method for tetrahydropyranylation/depyranylation of phenols and alcohols using a solid acid catalyst with Wells–Dawson structure

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Abstract—A simple and efficient procedure to form 2-tetrahydropyranyl acetals of phenols and alcohols is reported. Wells–Dawson heteropolyacid catalyst is used both in bulk form or supported on silica, reaction conditions include room temperature and toluene as solvent. Fast deprotection of THP-acetals can be attained by mere change of the solvent using THF–1% MeOH. In both reactions the supported catalyst is easily recoverable and reusable, and the yields are good to excellent. © 2002 Elsevier Science Ltd. All rights reserved.

Introduction and removal of protective groups is of great significance in organic synthesis.[1,2] Amongst various procedures available for the protection of hydroxyl groups, tetrahydropyranylation is the most frequently used because of the remarkable stability of tetrahydropyranyl acetals under a variety of conditions.[3] A number of catalysts have been used for tetrahydropyranylation[3] such as protic acids[4] and Lewis acids.[5] Besides, tetrahydropyranylation has been carried out using some heterogeneous catalysts, e.g. ion exchange resins,[6] zinc chloride on alumina, natural kaolinite clay and sulfuric acid adsorbed on silica gel;[7] heteropolyoxometallates[8] and heteropolyacids (HPAs).[9,10] Deprotection of tetrahydropyranyl derivatives has involved catalysts such as mineral acids,[11] organic acids, PPTS and Lewis acids,[11] heteropolyoxometallates[8] and HPAS;[10] other compounds have been recently used such as LiBr,[3] CBr_4/MeOH,[12] $Sc(OTf)_3$.[13] Amongst the heterogeneous catalysts, montmorillonite clays,[2] Amberlyst H-15[11] and sulfuric acid adsorbed on silica gel[7] have been used.

The problems associated with the handling and disposal of the inorganic acids, and their environmental and potential hazards have raised our interest in the development of alternative procedures using solid acid catalysts.[9,14] Due to their superacidic properties, HPAs can be used in reactions requiring electrophilic catalysis. HPAs are applied both in bulk or supported form, homogeneous and heterogeneous catalysis being possible. The structure of Wells–Dawson (WD) acid ($H_6P_2W_{18}O_{62}\cdot 24H_2O$) consists of a close-packed framework of octahedra WO_6 surrounding a central P atom, two identical 'half units' PW_9 are linked through the oxygen atoms.[15]

WD acid ($H_6P_2W_{18}O_{62(aq)}$) was prepared as described elsewhere[15] from an aqueous solution of α/β $K_6P_2W_{18}O_{62}\cdot 10H_2O$ salt, which was treated with ether and a concentrated (37%) HCl solution.

Silica-supported WD acid was obtained by wet impregnation of Grace Davidson silica (Grade 59, specific area = 250 m^2/g) with an aqueous solution of WD acid; a catalyst containing 20% (weight) of WD acid was prepared. After impregnation, catalyst samples were dried at room temperature in a vacuum-dessicator for 8 h.

Keywords: protecting group; tetrahydropyranyl; heteropolyacids; Wells–Dawson catalyst; alcohols; phenols.

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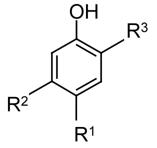
In general, the experiments involving catalyst supported on silica afforded similar yields to those obtained using bulk catalyst. However, use of the supported one allows for the easy separation and recovery of the catalyst for its immediate reutilization, without any lowering of its activity. For the checked examples, yields were practically unchanged over three reaction cycles. All yields were calculated from isolated products. Their purity was established by GLC, being better than 97% in all the cases.

The protection reaction was studied using phenols **1**–**8** and alcohols **9**–**13** as the substrates,[†] structure and substitution pattern are showed in Scheme 1. Different reaction conditions were checked: temperature, time and concentration of the solutions. The reaction was carried out using both bulk and supported WD catalysts; molar ratio of the WD acid to substrate was also varied.

To a mixture of phenol or alcohol (0.5 mmol) and DHP (1 mmol) in toluene (2 ml) WD catalyst (1% mmol) was added and stirred at room temperature for 2 h, see Table 1. The reaction mixture was filtered, washed (1 M NaOH and then H_2O but only for phenol substrates) and the solution was dried over anhydrous Na_2SO_4. Filtration and concentration followed by flash column chromatography on silica (hexanes–toluene) afforded THP-acetals. They were identified via comparison with authentic samples (TLC, GC).

Shorter reaction times cause lower yields of THP-acetal of **1** (**1**-THP), longer times also cause a lowering of the yields. When there is a nitro group at the phenyl ring, moderate yields are obtained, unmodified by prolonged reaction times; however, yields are at least good in the presence of other electron withdrawing groups.



1 – 6

Compounds	R^1	R^2	R^3
1	H	H	H
2	NO_2	H	H
3	OCH_3	H	H
4	Cl	H	H
5	CHO	H	OMe
6	H	Me	Pr^i

Compounds	
7	α-$C_{10}H_7OH$
8	β-$C_{10}H_7OH$
9	Ph-CH_2OH
10	Ph-CH_2CH_2OH
11	Ph-$CH(OH)CH_3$
12	Ph-$CH_2CH_2CH_2OH$
13	Ph-OCH_2CH_2OH

Scheme 1. Phenol and alcohol substrates.

Table 1. Tetrahydropyranylation of phenols and alcohols[a]

Phenol or alcohol	ROH:DHP molar ratio	% Yield	
		Bulk WD	Supported WD[b]
1	1:2	98	99 (98)
2	1:5	61	61
3	1:2	91	90
4	1:2	95	92 (92)
5	1:2	76	70
6	1:2	81	80
7	1:2	100	100 (98)
8	1:2	100	98
9	1:2	99	97
10	1:2	100	100 (99)
11	1:2	98	99
12	1:2	97	98
13	1:2	96	95

[a] Reactions were performed at 20°C in toluene, using 1% (mmol) of WD acid; reaction time 2 h.

[b] Yields in parentheses correspond to the second reutilization of the catalyst.

Removal of the THP group can be performed under mild reaction conditions, and the reaction proceeds in a few minutes. Hydrolysis of **1**-THP using 1% of bulk or supported catalyst in different solvents give the results shown in Table 2. When toluene was used, the reaction was slow and a maximum yield of 78% in 5 h was reached. Using THF, 94% yield was obtained in 2 h. Methanol dissolves the catalyst, yielding 100% after 15 min, therefore is a good solvent for the homogeneous reaction, but it is disadvantageous when supported catalyst is used because it dissolves the WD acid off the silica. Therefore, and taking into account recent results,[14] we examined the use of a THF plus 1% MeOH mixture, obtaining excellent yields. Besides, the use of supported WD acid afforded similar yields to those obtained with bulk catalyst. Deprotection of THP-acetals of compounds **2**–**13** was performed using standardized reaction conditions, see Table 3, giving clean reactions and yields better than 95% in all the examples.

Table 2. Deprotection of THP-acetal of phenol **1**[a]

Solvent	*t* (min)	% Yield	
		Bulk WD	Supported WD
MeOH	15	100	–
PhMe	300	78	78
THF	60	88	90
THF	120	94	94
1% MeOH/THF	5	91	71
1% MeOH/THF	10	100	94
1% MeOH/THF	15	100	99 (98)[b]

[a] Reactions were performed at 20°C using 1% (mmol) of WD acid and molar ratio ROH:DHP, 1:2.

[b] Yields in parentheses correspond to the second reutilization of the catalyst.

[†] Starting phenols and alcohols **1–13** were commercial, they were initially purified to match the reported physical data.

Table 3. Deprotection of THP-acetals of phenols and alcohols[a]

THP-acetal of	% Yield	
	Bulk WD	Supported WD[b]
2	99	94
3	98	97
4	100	98 (97)
5	96	95
6	95	95
7	98	96 (96)
8	96	95
9	98	98
10	99	97 (95)
11	100	99
12	100	98
13	98	99

[a] Reactions were performed at 20°C in THF–1% MeOH, using 1% (mmol) of WD acid. Reaction times: With bulk WD 10 min; with supported WD 15 min, excepted **2** (20 min) and **3** (12 min).

[b] Yields in parentheses correspond to the second reutilization of the catalyst.

The THP-acetal (0.5 mmol) was dissolved in THF–1% MeOH (2 ml), 1% WD catalyst was added and the mixture was stirred at room temperature for the stated time (Tables 2 and 3). The suspension was filtered, the solution was dried over anhydrous Na_2SO_4, filtered and concentrated, and the crude product was subjected to column chromatography (toluene–EtOAc) to yield the alcohol or phenol.

Conclusions

These procedures provide a useful alternative for the preparation of THP-acetals, as well as for their cleavage to the corresponding phenols or alcohols. Advantages of this methodology are: operational simplicity, no corrosive and reusable catalyst, mild conditions, short reaction times and excellent yields. The use of the solid catalyst allows replacement of the usual soluble inorganic acids, contributing to a reduction of waste.

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