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Part 148 in the Series "Studies on Novel Synthetic Methodologies:" Selective Acetylation of Alcohols, Phenols and Amines and Selective Deprotection of Aromatic Acetates using Silica-Supported Phosphomolybdic Acid

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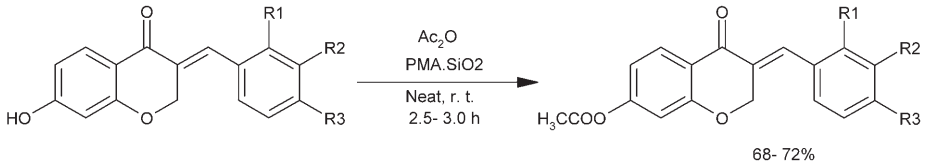
Abstract: An environmentally friendly silica-supported phosphomolybdic acid was found to be a highly efficient catalyst for the selective acetylation of alcohols, phenols and amines in the absence of any solvent and also for the chemoselective deprotection of aromatic acetates under very mild conditions. This method has been used for the protection of the hydroxy groups as well as for the deprotection of the acetates of several naturally occurring bioactive phenolic compounds. The catalyst can be easily recovered and reused.

Keywords: alcohols; amines; heterogeneous catalysts; protecting groups; silica-supported phosphomolybdic acid; solvent-free conditions

Protection of functional groups is highly essential in organic synthesis. Alcohols, phenols and amines are frequently protected as acetates, which are generally prepared by reaction with Ac_2O in the presence of pyridine.[1] 4-(Dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY) are also known to catalyze the acetylation of alcohols.[2] Several Lewis acids, such as metal halides,[3] metal triflates[4] and microwave irradiation[5] have recently been introduced for the preparation of acetates from alcohols and phenols. However, many of these methods are associated with one or more drawbacks such as non-availability of the reagents, harsh reaction conditions, long reaction times, unsatisfactory yields and disturbance to other functional groups. Moreover, the selectivity of acetylation is also important in multistep syntheses. Thus, a suitable, efficient and selective method for the acetylation of alcohols, phenols and amines would be highly useful.

In recent years, heterogeneous catalysts have gained considerable importance due to environmental and economic considerations. In continuation of our work[6] on the application of the heterogeneous catalysts for the development of useful synthetic methodologies, we have observed that silica-supported phosphomolybdic acid[7] is very suitable to catalyze the acetylation of alcohols and phenols with acetic anhydride to form the corresponding acetates at room temperature (Scheme 1).This catalyst is important from an environmental point of view as it possesses excellent activity, low toxicity and high stability towards humidity. It can be recovered from the reaction mixture and reused.

The catalytic activity of silica-supported phosphomolybdic acid was determined initially by preparing acetyl-3-methoxyphenol in high yield (78%) from the reaction of 3-methoxyphenol and acetic anhydride using the catalyst in CH_2Cl_2 at room temperature within 3.0 h. (Table 1, entry 1). We used different solvents such as $CHCl_3$, CH_2Cl_2, THF, MeCN or Et_2O for the reaction but the conversion proceeded best



Scheme 1.

Table 1. Acetylation of alcohols, phenols and amines using silica-supported phosphomolybdic acid under solvent-free conditions.

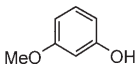
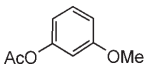
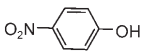
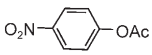
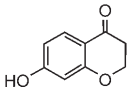
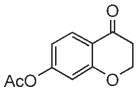
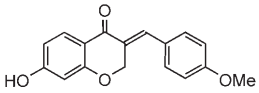
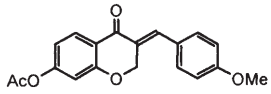
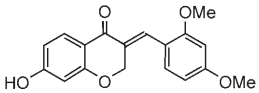
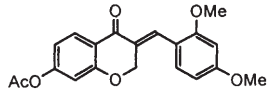
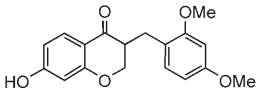
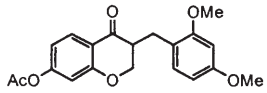
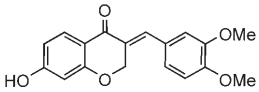
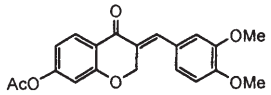
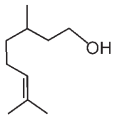
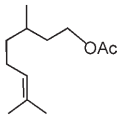
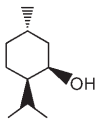
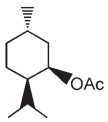
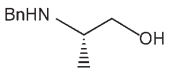
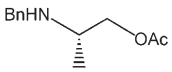
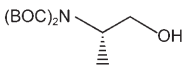
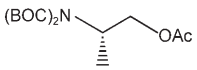
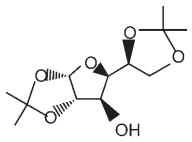
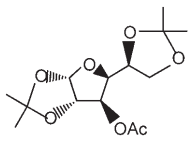
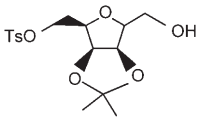
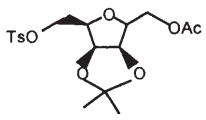
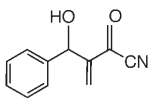
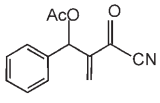
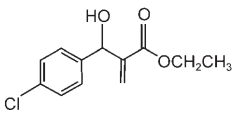
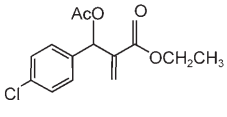
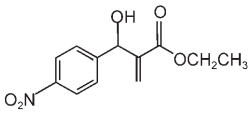
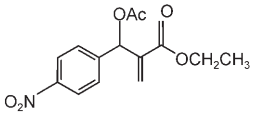
Entry	Substrate	Product[a]	Time[b] [h or min]	Yield[c] [%]
1			3.0	72
2			3.5	70
3			3.0	71
4			3.0	70
5			3.0	68
6			3.0	69
7			2.5	72
8			8	96
9			10	98
10			10	97
11			8	94
12			10	96
13			12	95
14			10	92
15			10	95
16			8	93

Table 1. (Continued)

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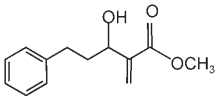
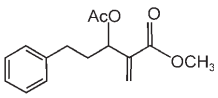
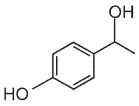
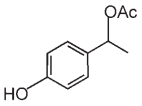
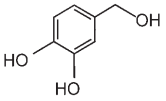
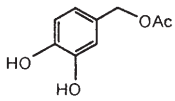
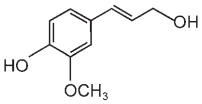
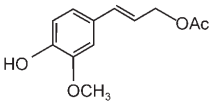
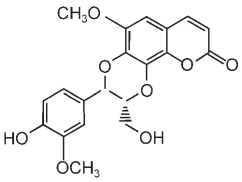
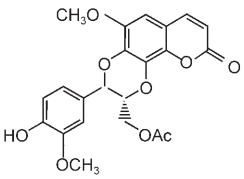
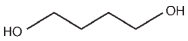
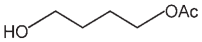
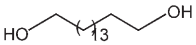
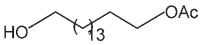
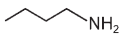
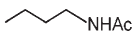
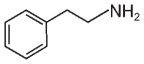
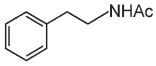
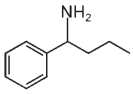
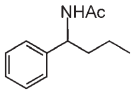
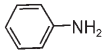
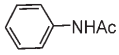
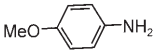
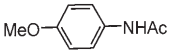
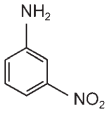
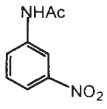
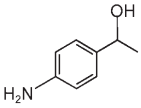
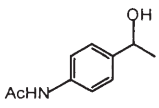
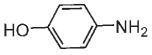
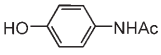
17			10	91
18			12	97
19			10	95
20			10	96
21			10	98
22			8	94
23			8	95
24			8	93
25			10	96
26			8	93
27			10	90
28			12	92
29			15	95
30			10	91
31			13	94

[a] All the compounds were characterized by ^{1}H NMR and mass spectral data.
[b] Reaction times for entries 1–6 are in h, those for entries 7–31 in min.
[c] Isolated yields after column chromatography.

under solvent-free conditions. In the absence of the catalyst the product was not formed while in the absence of phosphomolybdic acid and only with SiO_2 the transformation took a long time and the yield was only 12 % after 5 h.

A wide variety of phenols (mono- and bicyclic), alcohols (aromatic, aliphatic, primary, secondary, allylic and benzylic) and amines (aromatic and aliphatic) were converted into their corresponding acetates in excellent yields (Table 1). The conversion was com-

plete within 8–15 min. In the present case the acetylation of alcohols was carried out keeping intact other hydroxy and amine protecting groups, such as benzyl (Table 1, entry 10), tosyl (entry 13), BOC (entry 11) and acetonide (entries 12 and 13). The isomerization of an unsaturated alcohol (entry 20) and epimerization of a chiral alcohol (entry 9) were not observed. Phenols having both electron-donating as well as electron-withdrawing substituents underwent the reaction smoothly giving the desired products in moderate to good yields (the results are summarized in Table 1). Several naturally occurring compounds having phenolic hydroxy groups were also transformed into the corresponding acetates (entries 4–7). Another application of the present method is the preparation of Baylis–Hillman acetates from the corresponding adducts (entries 14–17). Baylis–Hillman acetates are useful for the synthesis of stereo-defined trisubsiituted alkenes.[8] However, on acetylation with Ac_2O-pyridine Baylis–Hilaman adducts generally form isomeric acetates along with normal acetylation products.[9] This problem can be solved by acetylation of the adducts with Ac_2O catalyzed by silica-supported phosphomolybdic acid.

The chemoselectivity of the present acetylation method is remarkable. An alcoholic hydroxy group can conveniently be acetylated keeping intact the phenolic hydroxy group in a molecule (entries 18 and 21) within 8–15 min (when both reactants are in a 1:1 ratio). If the reaction was carried out using excess of Ac_2O the diacetyled product (entry 18) was obtained in less yield (34%) after 3 h. This selectivity is highly important to carry out modifications to two different types of hydroxy groups at different stages of a reaction sequence. Acetylation of symmetrical diols using silica-supported phosphomolybdic acid under the present experimental conditions afforded only the monoacetates (entries 22 and 23) in excellent yields. The selective monoacetylation of these symmetrical diols is possibly due to the preferential adsorption of these compounds, but not monoacetates, on the surface of the used catalyst where acetylation takes place.[10] When in a molecule both hydroxy and amine groups were present (entries 30 and 31) only the amine group was protected selectively. The interesting selectivity of the present method can be utilized for the preparation of bioactive natural products. Thus, cleomiscosin A, a natural anticancer agent, was directly converted into another natural coumarinolignan, venkatasin[11] (entry 21) by acetylation with Ac_2O in the presence of silica-supported phosphomolybdic acid. Anilines containing both electron-withdrawing groups (entry 29) and electron-donating groups (entry 28) in the aromatic ring underwent acetylation smoothly. Acetylation of aliphatic amines (entries 24 and 26) was somewhat faster than that of anilines (entries 27–31).

Phenolic hydroxy groups are present in several bioactive naturally occurring compounds. Hence protection and subsequent deprotection of this group is necessary for multistep transformations and synthesis of these compounds.[1] Deprotection of aromatic acetates can be carried out under acidic, basic or hydrogenation conditions.[1] However, the deprotection methods may effect several sensitive functional groups present in the molecules. A limited number of methods exist for the selective deprotection of aromatic acetates in the presence of aliphatic acetates.[12] Although these methods have certain applicabilities, most of them have certain drawbacks such as operational complexity, harsh conditions, use of costly reagents, long reaction times and low yields. The recovery of the catalyst is also a problem.

We have observed that silica-supported phosphomolybdic acid is a highly efficient catalyst for selective deprotection of aromatic acetates in methanol at room temperature within 2–3 h. Several aromatic acetates underwent deprotection in the presence of the catalyst to produce the corresponding parent phenols (Table 2). The yields of regenerated phenols were typically excellent. We also used various other solvents such as THF, $CHCl_3$, CH_2Cl_2, MeCN, and Et_2O for the reaction but the conversion proceeded best in the presence of methanol. Alkyl acetates were uneffected by the catalyst under the present experimental conditions. The catalyst showed similar activity towards the deprotection of aromatic acetates containing electron-donating and electron-withdrawing groups (results are summarized in Table 2).

The present methodology has been applied for deprotection of acetyl derivatives of several bioactive natural products. Thus acetylbonducellin (entry 7), triacetylsappanone (entry 11), acetyl-2′-methoxybonducellin (entry 8), acetyl-2′-methoxydihydrobonducellin (entry 10), diacetyl-3′-methoxybonducellin (entry 9), and scopoletin (entry 15) underwent deacetylation efficiently to form the corresponding parent phenols. Rhododendol diacetate and cleomiscosin A diacetate afforded rhododendol monoacetate (entry 18) and venkatasin (entry 19), respectively, with chemoselective regeneration of phenolic hydroxy groups in very high yields (Scheme 2).

In conclusion, we have developed a simple and efficient method for acetylation of alcohols, phenols and amines with Ac_2O using silica-supported phosphomolybdic acid as a heterogeneous catalyst. The catalyst has also been applied for the deprotection of aromatic acetates. The salient features of this protocol include operational simplicity, mild reaction conditions, short reaction times, excellent yields, application of an inexpensive heterogeneous catalyst, compatibility with other hydroxy and amine protecting groups, high chemoselectivity and monoprotection of symmetrical diols. The method is quite suitable for the direct prep-

Table 2. Deprotection of aromatic acetates using silica-supported phosphomolybdic acid.

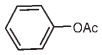
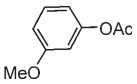
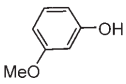
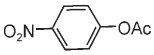
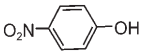
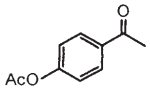
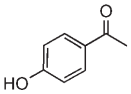
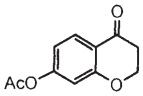
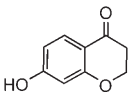
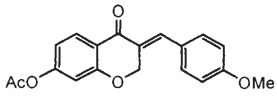
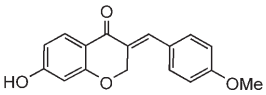
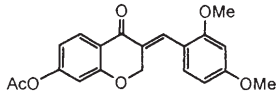
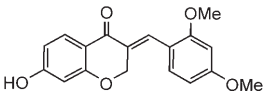
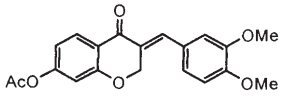
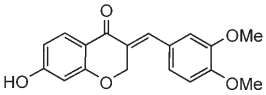
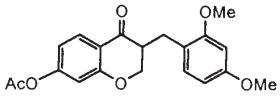
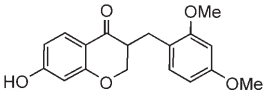
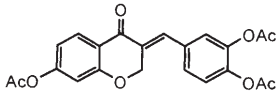
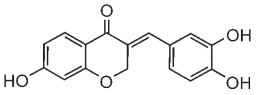
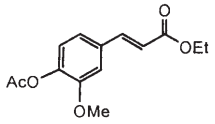
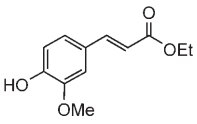
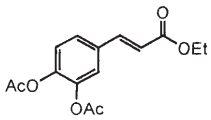
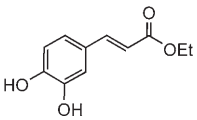
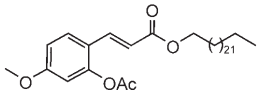
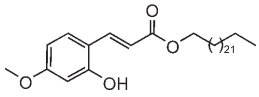
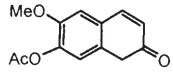
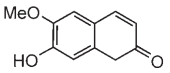
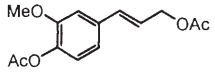
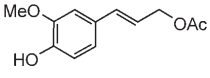
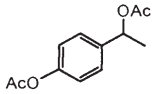
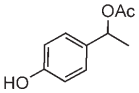
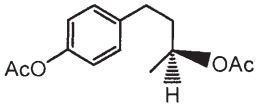
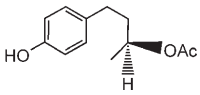
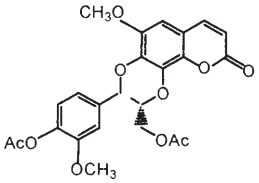
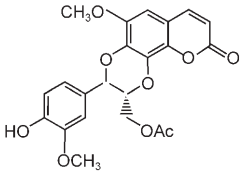
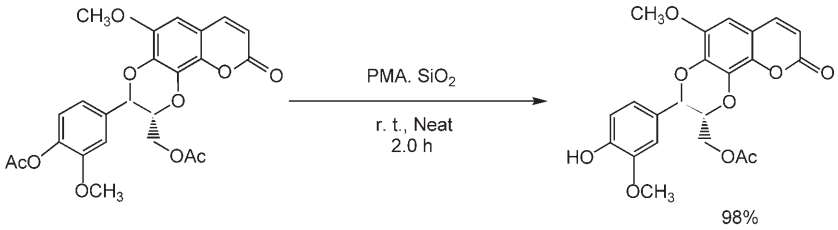
Entry	Substrate	Product[a]	Time [h]	Yield[b] [%]
1			2.0	98
2			2.0	96
3			2.5	96
4			3.0	89
5			2.0	95
6			2.0	96
7			2.5	93
8			2.5	94
9			2.5	96
10			2.0	92
11			2.7	95
12			2.0	96
13			2.5	94
14			2.8	90
15			3.0	94
16			2.0	97
17			2.5	98

Table 2. (Continued)

Entry	Substrate	Product[a]	Time [h]	Yield[b] [%]
18			2.5	95
19			2.0	98

[a] All the compounds were characterized by ^{1}H NMR and mass spectral data.
[b] Isolated yields after column chromatography.



Scheme 2.

aration of venkatasin, a natural coumarino-lignan from anticancer agents, cleomiscosin A and for the preparation of Baylis–Hillmans acetates from the corresponding adducts without simultaneous isomerization. The catalyst was reused without any pretreatment. The efficiency and stability of the catalyst were found to be good even after three cycles.

Experimental Section

Acetylation of Alcohols, Phenols and Amines

To a mixture of an alcohol, phenol or amine (1 mmol) and Ac_2O (1.5 mmol) under solvent-free conditions silica-supported phosphomolybdic acid (113 mg) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion of the reaction the mixture was filtered and the catalyst was recovered after washing the residue with methanol (2×5 mL). The filtrates was concentrated and the residue was subjected to column chromatography (silica gel, 20% EtOAc in hexane) to obtain the pure acetate. The recovered catalyst was reused three times subsequently for the same reaction without affecting the yield of the product.

Selective Deprotection of Aromatic Acetates

Aryl acetate (1 mmol) and silica-supported phosphomolybdic acid (113 mg) were taken in MeOH (5 mL). The mixture was stirred at room temperature and the progress of the reaction was followed by TLC. After completion of the reaction the catalyst was filtered off and washed with MeOH (2×5 mL). The filtrate was concentrated and extracted with EtOAc (3×8 mL). The concentrated extract was purified by column chromatography (silica gel, 35% EtOAc in hexane) over silica gel to afford the parent phenol. The recovered catalyst was also used here consequently three times and the yield was found to be unaffected.

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