

Tungstophosphoric acid ($\text{H}_3\text{PW}_{12}\text{O}_{40}$) as a heterogeneous inorganic catalyst. Activation of hexamethyldisilazane (HMDS) by tungstophosphoric acid for efficient and selective solvent-free *O*-silylation reactions

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Tungstophosphoric acid ($\text{H}_3\text{PW}_{12}\text{O}_{40}$) effectively activates hexamethyldisilazane for the selective silylation of primary, secondary, tertiary and phenolic hydroxy groups under solvent-free conditions at 55–60 °C.

Introduction

Uses of heteropolyacids (HPAs) as catalysts for fine organic synthetic processes have been developed that are very important for industries related to fine chemicals, such as flavors, pharmaceuticals and food industries.¹ Heteropolyacids are more active catalysts than conventional inorganic and organic acids for various reactions in solution.² They are used as industrial catalysts for several liquid-phase reactions,^{3–6} such as alcohol dehydration,⁷ alkylation,⁸ and esterification⁹ reactions. Among heteropolyacids, polytungstic acids are the most widely used catalysts owing to their high acid strengths, thermal stabilities, and low reducibilities. Catalysts based on heteropolyacids have many advantages over liquid acid catalysts. They are non-corrosive and environmentally benign, presenting fewer disposal problems. Their repeated use is possible and their separation from liquid products is easier than for the homogeneous catalysts.¹⁰

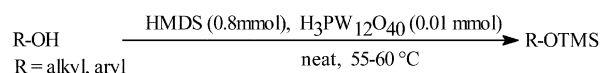
We have recently started studies on the catalytic properties of heteropolyacids, especially tungstophosphoric acid ($\text{H}_3\text{PW}_{12}\text{O}_{40}$) which is a cheap, reusable, heterogeneous and easy available catalyst. We have already used this catalyst for the oxidation of aromatic amines to nitro compounds with sodium perborate in micellar media, thioacetalization and transthioacetalization reactions, its caesium salt for regioselective bromination of aromatic compounds and oxidation of hydroxy groups to their corresponding carbonyl functions with $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ activated by $\text{H}_3\text{PW}_{12}\text{O}_{40}$.¹¹

Protection of the hydroxy functional group is an important process in multi-step synthesis. One of the popular methods for this purpose is to transfer hydroxy groups of their corresponding silyl ethers. Hexamethyldisilazane (HMDS) is a cheap and commercially available compound that can be used for the preparation of trimethylsilyl ethers from hydroxy compounds. Even though the handling of this reagent is easy, its main drawback is its poor silylating power which needs forceful conditions and long reaction times.¹² For the activation of HMDS, a variety of catalysts have been reported.¹³ Recently iodine has also been used as an effective catalyst for the activation of HMDS in silylation reactions.¹⁴

Solvent-free reactions have attracted considerable attention in chemical processes for different reasons. They are valuable due to environmental safety, the economic viewpoint, easy work-up, high yields of the products and (usually) their fast reaction times.¹⁵

In continuation of our work on the catalytic properties of heteropolyacids, herein we report the use of tungstophosphoric

acid ($\text{H}_3\text{PW}_{12}\text{O}_{40}$) as a reusable and heterogeneous catalyst for efficient and selective *O*-trimethylsilylation of a wide variety of alcohols and phenols using easily available hexamethyldisilazane (HMDS) at 55–60 °C under solvent-free conditions (Scheme 1).



Scheme 1

Results and discussion

Primarily as a model reaction, silylation of benzyl alcohol with HMDS was performed in the presence of several heteropolyacids and their salts, and some other acids at 55–60 °C under solvent-free conditions (Table 1). In order to show the strong catalytic activity of heteropolyacids and their salts in comparison with other acids, we studied the catalytic activities of HY-zeolite, Amberlyst-15, triflic acid and sulfuric acid for this purpose. The results show that in the presence of most of the heteropolyacids, silylation reactions proceeded efficiently (Table 1, entries 1–6). The results show that tungstophosphoric acid, $\text{H}_3\text{PW}_{12}\text{O}_{40}$, a commercially available and cheap crystalline compound, was the most effective catalyst for this purpose and it was used in 0.01 molar equivalents for the silylation of other hydroxy compounds throughout this study (Table 1, entry 2). The observed catalytic activity of $\text{H}_3\text{PW}_{12}\text{O}_{40}$ with Hammett acidity function $H_0 < -13.16$ reflects the stronger acidity strength of this compound in comparison with, for example, H_2SO_4 $H_0 = -12$.¹⁶ Recently an acidity scale for Brønsted acids including $\text{H}_3\text{PW}_{12}\text{O}_{40}$ was reported in the literature.¹⁷ The reported results show the acidity strength follows the order: $\text{H}_3\text{PW}_{12}\text{O}_{40} > p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H} \approx \text{H}_2\text{SO}_4$.

We have found that $\text{H}_3\text{PW}_{12}\text{O}_{40}$ is a reusable catalyst and even after ten runs for the silylation of benzyl alcohol with HMDS, the catalytic activity of $\text{H}_3\text{PW}_{12}\text{O}_{40}$ was almost the same as that of the freshly used catalyst. This method can be applied to liquid or crystalline alcohols and phenols without any difficulties.

We have applied similar reaction conditions for the silylation of primary and secondary benzylic alcohols. Reactions proceeded efficiently with high isolated yields (Table 2, entries 1–7). Primary and secondary aliphatic alcohols were also converted to their corresponding silyl ethers under similar reaction conditions with excellent yields (Table 2, entries 8–10). This method was found to be useful for the protection of hindered secondary and tertiary alcohols (Table 2, entries 11–15). Phenol, 4- $\text{ClC}_6\text{H}_4\text{OH}$ and 4- $\text{MeCOC}_6\text{H}_4\text{OH}$ were also silylated easily and their corresponding silyl ethers were isolated in 95%, 85%, and 87% yields respectively (Table 2, entries 16–18). 4- $\text{NO}_2\text{C}_6\text{H}_4\text{OH}$ with a strongly electron-attracting group remained intact under

Table 1 Silylation of benzyl alcohol using HMDS in the presence of various heteropolyacids, their salts and some other acids at 55–60 °C under solvent-free conditions

Entry	Catalyst	Substrate : HMDS : catalyst	Time/min	Yield (%)
1	H ₃ PW ₁₂ O ₄₀	1 : 0.8 : 0.01	210	100 ^a
2	H ₃ PW ₁₂ O ₄₀	1 : 0.8 : 0.01	23	100
3	H ₄ SiPW ₁₂ O ₄₀	1 : 0.8 : 0.0075	40	98
4	H ₄ PMo ₁₂ O ₄₀ · <i>n</i> H ₂ O	1 : 0.8 : 0.0075	26	100
5	Ni ₃ (PW ₁₂ O ₄₀) ₂	1 : 0.8 : 0.01	80	90
6	Cu ₃ (PW ₁₂ O ₄₀) ₂	1 : 0.8 : 0.01	85	90
7	HY Zeolite	1 : 0.8 : 0.1 g	120	80
8	Amberlyst-15H ⁺	1 : 0.8 : 0.1 g	120	60
9	CF ₃ SO ₃ H	1 : 0.8 : 0.03	65	90
10	TsOH	1 : 0.8 : 0.03	35	98
11	H ₂ SO ₄	1 : 0.8 : 0.015	40	96

^a The reaction was carried out at room temperature.**Table 2** Silylation of alcohols and phenols using HMDS in the presence of H₃PW₁₂O₄₀ at 55–60 °C under solvent-free conditions

Entry	ROH	Time/min	Yield (%) ^a
1	PhCH ₂ OH	23	90
2	4-ClC ₆ H ₄ CH ₂ OH	7	82
3	4-MeC ₆ H ₄ CH ₂ OH	6	95
4	4-OMeC ₆ H ₄ CH ₂ OH	20	96
5	PhCH(OH)CH ₃	16	93
6	PhCH(OH)CH ₂ CH ₃	15	95
7	PhCH(OH)Ph	48	93 ^b
8	PhCH ₂ CH ₂ CH ₂ OH	18	92
9	Octan-1-ol	7	96
10	Octan-2-ol	9	93
11	<i>tert</i> -Butyl alcohol	30	94
12	Adamantan-1-ol	135	90
13	(-)-Menthol	8	92
14	Norborneol	30	90
15	Terpeneol	120	96
16	PhOH	12	95
17	4-ClC ₆ H ₄ OH	3	85
18	4-MeCOC ₆ H ₄ OH	30	87
19	4-NO ₂ C ₆ H ₄ OH	120	0
20	2-Naphthol	6	90
21	PhNH ₂	120	0
22	PhCH ₂ SH	160	0
23	PhCOOH	180	0
24	Geraniol	60	— ^c
25	Cinnamyl alcohol	45	— ^c
26	Oct-3-en-1-ol	55	— ^c
27	Hex-3-yne-2,5-diol	80	— ^c

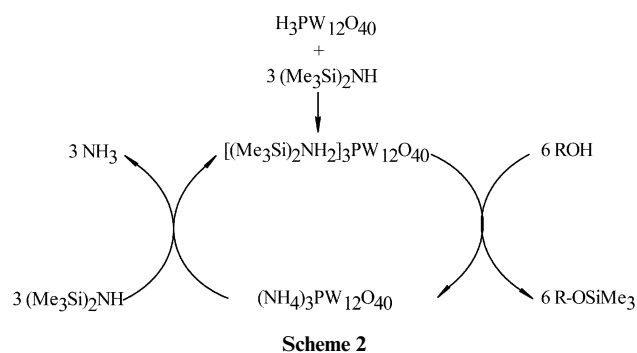
^a Isolated yields. ^b Reaction proceeded more easily in the presence of 1 ml of *n*-hexane. ^c Unidentified polymeric material was isolated.

similar reaction conditions (Table 2, entry 19). 2-Naphthol was also silylated under similar reaction conditions with 90% yield within 6 min (Table 2, entry 20). Aniline, benzyl thiol and benzoic acid remained intact in the reaction mixture even after prolonged reaction times (Table 2, entries 20–22). We found that this method was not suitable for the protection of allyl and propargyl alcohols, polymeric materials being produced in their reaction mixtures (Table 2, entries 24–27).

Selectivity of a method is important in the multi-step preparation of organic compounds and provides a broad spectrum for its uses in functional group transformation reactions. Therefore, we tried several competitive reactions under similar conditions in order to show the scope and limitation of this catalytic system. By this system, a primary benzylic hydroxy group can be protected in the presence of a secondary aliphatic alcohol with the ratio of 80 : 20 [Table 3, eqn. (1)]. A secondary aliphatic alcohol was protected in the presence of a secondary benzylic alcohol with the ratio of 80 : 20 [Table 3, eqn. (2)]. A secondary aliphatic alcohol in the presence of a tertiary alcohol was protected with the ratio of 95 : 5 [Table 3, eqn. (3)]. Reaction of 3-aminophenol was also studied to investigate the selectivity of the method. It was observed that the phenolic

functional group was quantitatively protected in the presence of an amino group [Table 3, eqn. (4)]. The selectivity of the method in a single molecule carrying primary and secondary hydroxy groups has also been demonstrated [Table 3, eqn. (5)]. The percentage of the products in the reaction mixture was determined by GC analysis. The products were separated by column chromatography using EtOAc–*n*-hexane (1 : 9) as an eluent. The major product (**5a**) was identified by the mild oxidation of the hydroxy group to 4-(trimethylsilyloxy)butan-2-one (**5c**). The spectral data of compound **5c** are given in the Experimental section.

In all reactions in this study, generation of ammonia gas (NH₃) from the reaction mixtures can be detected easily. In the reaction mixtures, H₃PW₁₂O₄₀ as a strong acid, reacts with HMDS to produce [(Me₃Si)₂NH]₃PW₁₂O₄₀ salt. This salt in turn reacts with alcohol molecules to produce the corresponding silyl ethers plus an ammonium salt of tungstophosphoric acid [(NH₄)₃PW₁₂O₄₀]. In order to study qualitatively the probable reaction pathway of these reactions, we prepared highly thermally stable ammonium dodecatungstophosphate (NH₄)₃PW₁₂O₄₀ according to the literature procedure.¹⁸ Then the reaction of HMDS molecules with [(NH₄)₃PW₁₂O₄₀] was studied. We observed that HMDS reacts immediately with [(NH₄)₃PW₁₂O₄₀] to produce ammonia gas plus a greyish white solid compound. This solid compound as a reagent can easily convert alcohols to their corresponding silyl ethers. In experiments, we have also studied the reactions of ammonium salt of dodecatungstophosphoric acid [(NH₄)₃PW₁₂O₄₀] as a catalyst with HMDS in the presence of several alcohols. The reactions proceeded easily with the evolution of ammonia gas and the production of the corresponding silyl ethers. With this information in mind we propose a catalytic reaction cycle in which the production of [(Me₃Si)₂NH]₃PW₁₂O₄₀ and [(NH₄)₃PW₁₂O₄₀] as catalysts and production of silyl ethers and ammonia gas as the products of the reactions are clarified (Scheme 2).



In conclusion, in this study we have introduced a new catalytic application of tungstophosphoric acid H₃PW₁₂O₄₀ as the activator of HMDS for the efficient protection of a variety of alcohols and phenols under solvent-free conditions.

By this method, bulky secondary and tertiary hydroxy functional groups were protected efficiently with excellent yields.

Table 3 Competitive silylation reactions of alcohols using HMDS in the presence of $\text{H}_3\text{PW}_{12}\text{O}_{40}$ at 55–60 °C under solvent-free conditions

1	
2	
3	
4	
5	

The method shows reasonably high selectivity among different hydroxy and amine functional groups. The catalyst is a heterogeneous, recyclable, non-corrosive and environmentally benign compound. Isolation of the product from a heterogeneous reaction mixture is much easier than from a homogeneous system and by a simple extraction and evaporation of the solvent, the pure product could be isolated. The catalytic activity of $\text{H}_3\text{PW}_{12}\text{O}_{40}$ was found to be much higher than that of HY-zeolite, Amberlyst-15, triflic acid, toluene-*p*-sulfonic acid and sulfuric acid.

Experimental

General

Chemicals were either prepared in our laboratories or were purchased from Fluka or Merck. Heteropolyacid ($\text{H}_3\text{PW}_{12}\text{O}_{40}$) was purchased from Merck and was purified by the literature method.¹⁹ The purity determination of the products was accomplished by GC on a Shimadzu model GC-14A instrument or by TLC on silica gel polygram SIL G/UV 254 plates. The FTIR spectra were recorded on a Shimadzu model 8300 instrument. The NMR spectra were recorded on a Bruker Advance DPX 250 MHz spectrometer.

General procedure for silylation of alcohols using HMDS catalyzed with tungstophosphoric acid

Alcohol (1 mmol), HMDS (0.8 mmol) and the catalyst (0.01 mmol, 0.028 g) were mixed and heated at 55–60 °C for the appropriate reaction time (Table 2). After completion of the reaction (monitored by TLC and GC), *n*-hexane (5 ml) was added and the catalyst was recovered by filtration and was washed with *n*-hexane (2 × 5 ml). The filtrate was then washed with water (10 ml) to destroy the extra amounts of HMDS and the organic layer was dried over anhydrous Na_2SO_4 . Evaporation of the solvent under reduced pressure gave the highly pure product without further purification.

4a: ^1H NMR (250 MHz, CDCl_3): δ = 3.58 [s, 2H (NH_2)], 6.2–6.53 [m, 5H (Ph)], 0.17 [s, 9H (TMS)]; IR (KBr): 3382, 3478, 1600, N–H, 1253 (O–TMS) cm^{-1} .

5a: ^1H NMR (250 MHz, CDCl_3): δ = 1.09 (d, 3H, CH_3 –CHOH), 3.45–3.58 (m, 1H, –CH–OH), 3.8 (s, 1H, –OH), 1.32–1.66 (m, 2H, $\text{CH}_3\text{CH}(\text{OH})$ – CH_2 – CH_2 –OTMS), 3.6 (t, 2H,

CH_2 –OTMS), 0.06 [s, 9H, –OSi(CH_3)₃]; IR (KBr): 3442 (OH), 1251 (OTMS) cm^{-1} .

5c: ^1H NMR (250 MHz, CDCl_3): δ = 0.06 [s, 9H, OSi(CH_3)₃], 3.47 (t, 2H, CH_2 –OTMS), 2.48 (t, 2H, CH_2 –CO), 2.25 (s, 3H, CH_3 –CO); IR (KBr): absence of OH absorption, 1643 (CO), 1251 (OTMS) cm^{-1} .

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