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$H_3PMo_{12}O_{40}$ as a new and reusable catalyst for Mukaiyama and Mannich reactions in heterogeneous media

Akbar Heydari [a,*], Samad Khaksar [a], Mehdi Sheykhan [a], Mahmoud Tajbakhsh [b]

[a] *Chemistry Department, Tarbiat Modares University, P.O. Box 14155-4838, Tehran, Iran*
[b] *Chemistry Department, Mazandaran University, Babol Sar, Iran*

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ABSTRACT

In the presence of a catalytic amount of $H_3PMo_{12}O_{40}$ (2 mol%) ketene silyl acetal react with aldehydes or imines (generated *in situ* from aldehydes and amines) to yield the corresponding coupling products in good yield.

1. Introduction

The application of heterogeneous acid catalysts in place of homogeneous acid catalysts in organic synthesis is an attractive area of research in the laboratory as well as in the industrial context. The advantages of the heterogeneous catalysts over the homogeneous catalysts include stability (toward air and moisture), lack of corrosion, ease of handling, recovery and regeneration [1]. Heteropoly acids (HPAs), especially those of the Keggin series, are widely used under both homogeneous and heterogeneous as catalysts for the synthesis of fine and specially chemicals [2]. HPAs show the very strong Brønsted acidity values, approaching the super acid region. Due to their stronger acidity, they generally exhibit higher catalytic activities than conventional catalysts, such as mineral acids, ion-exchange resins, zeolites, etc. in both heterogeneous and homogeneous systems [3]. As found recently, Keggin-type heteropoly acids, e. g., $H_3PW_{12}O_{40}$ (PW), $H_3PMo_{12}O_{40}$ (PMo) and $H_4SiW_{12}O_{40}$ (SiW) have been extensively studied because they are highly solid acid catalysts in homogeneous solutions, liquid–solid and gas–solid heterogeneous reactions. They can be separated and reused [4].

2. Results and discussion

The Mukaiyama aldol reaction (Lewis acid-promoted carbonyl addition of silyl enol ethers) has become a fundamental method of carbon–carbon bond forming reactions in modern organic synthesis [5]. It is well known that the reaction between carbonyl compounds and silyl enol ethers could proceed under various conditions [6]. For example, several efficient activator such as a fluoride ion [7] (nucleophilic cleavage of the O–Si bond), trityl salts [8], transition metal salts [9], HMPA derivatives [10], phosphine [11], thiourea [12], ionic liquids [13], Sn-MCM-41 [14], *N*-methylimidazole [15], *N*-heterocyclic carbenes [16] have been developed. Moreover, the reactions of ketene silyl acetals with aldehydes were carried out in water [17], elevated temperatureb [18] or under high-pressure [19]. Thus, it was considered important to explore a new and catalytic crossed aldol reaction of the above combination which is to be carried out smoothly under recyclable catalytic conditions.

Recent studies from our group have shown that one-pot three component Mannich-type reactions (amino reduction [20] and

* Corresponding author. Fax: +9821/88006544.
E-mail address: akbar.heydari@gmx.de (A. Heydari).

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Table 1
Reaction of benzaldehyde (**1a**) with ketene silyl acetal (**2**) catalyzed by various Keggin heteropoly acids at r. t. for 2 h in acetonitril

Entry	Catalyst (5 mol%)	Product yield (%)[a]
a	$H_3PW_{12}O_{40}$	60
b	$H_3PMo_{12}O_{40}$	95
c	$H_4SiW_{12}O_{40}$	70

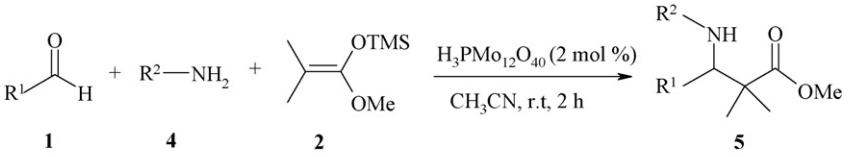
[a] Isolated yield.

amino phosphonylation [21]) proceed smoothly to afford the corresponding amines and α-amino phosphonates in the presence of PW, a well established stable Brønsted acid. In the course of our investigations to search for an effective catalyst for β-hydroxy ester synthesis from carbonyls and ketene silyl acetals, various Keggin-type heteropoly acids were screened. First, the possibilities of various Keggin-HPAs as catalysts were examined by taking the reaction of benzaldehyde (**1a**) and ketene silyl acetal (**2**) as a model (Table 1, entries a–c). Of various Keggin-HPAs screened, the use of a catalytic amount of PMo, despite the fact that PMo is a weaker acid compared to PW, gave the corresponding β-hydroxy esters in the best chemical yield (95%) (Table 1, entry b). The reasons for this effect is not clear at this time, however, it seem to be considerably conclude that the catalytic effect of HPAs in this reaction depends mainly on three factors, namely, the acidity, the softness of heteropolyanion and strongly type of reaction (nature of reagents). Thus, it observed that PW is a very active catalyst for alkylation of benzene with 1-octene. In contrast, PMo is the most efficient catalyst in alkylation of arenas with benzyl chloride or SiW is more active for the reaction of dibutyl ether with acetic anhydride than PW [3]. Generally, solid HPAs form ionic crystals composed of heteropolyanions, counterions (H^+, H_3O^+, $H_5O_2^+$, etc.) and hydration water. This water can be easily removed on heating, whereby the acid strength is increased due to the dehydration of protons. Investigation the kinetics (the products yields) as a function of the number of hydration water in HPAs is in progress.

The effect of the catalysts loading was examined in the test reaction, using PMo at 25 °C in acetonitrile (AN). When the reaction was carried out with 2% of PMo the product was obtained with the best yield β-hydroxy ester (**3a**). Furthermore, various aldehydes were treated with ketene silyl acetal (**2**) in the presence of catalytic amount of PMo in order to study the present reaction. The corresponding β-hydroxy esters **3a-g** was obtained in good yields. Replacing the aldehydes by a ketone has not been successful as no conversion was observed in the reaction of acetophenone with ketene silyl acetal (**2**) in the presence of PMo. In view of "green chemistry", reuse of catalyst is preferable. In reaction of benzaldehyde (**1a**) with ketene silyl acetal (**2**), the PMo was separated by simple filtration and reused with only a gradual decrease in activity observed.

β-Lactams are compounds of primary importance as they are components of many naturally occurring antibiotics, such as penicillin, cephalosporin, thienamycine, etc. Consequently, many efforts have been done in last decades to develop new strategies in the construction of β-amino esters or azetidinone ring. The reaction of ketene silyl acetals with imines forming β-amino esters frequently employed as useful precursors in the synthesis of β-lactams. Although the reactions generally requires a stoichiometric amount of Lewis acid such as $TiCl_4$ [22], a catalytic amount of TMSOTf [23], FeI_2 [24], diphosphine salt [25], trityl salt [24], montmorillonite [26] and $B(C_6F_5)_3$ [27] promotes the reactions. On the other hand, many imines are hydroscopic, unstable at high temperature and difficult to purify by distillation or column chromatography. It is desirable from a synthetic point of view that imines, generated *in situ* from aldehydes and amines, immediately react with ketene silyl acetals to provide β-amino esters in a one-pot reaction [28]. However, most Lewis acids cannot be used in this reaction, because they decompose or deactivate in the presence of the amines and water that exist during imine formation.

Recently, we found that HPAs effectively can be used for activation of nitrogen-containing compounds [20,21]. Moreover, it is stable and can be recovered after the reactions are completed and reused. Judging from these unique properties of HPAs, we planned to use it as catalyst for the one-pot three component preparation of β-amino esters from aldehydes. A general scheme of the one-pot synthesis of β-amino esters from aldehydes is shown in Scheme 1. In the presence of 2 mol% of PMo, the three component coupling reaction involving benzaldehyde (**1a**), aniline (**4**) and ketene silyl acetal (**2**) successively proceeded smoothly in AN at r. t. to afford the corresponding β-amino ester derivative in 95% yield. The new methodology allowed us to prepare the β-amino esters shown in Scheme 1. This one-pot process can be defined as Mannich reaction between imines and ketene silyl acetal. Aliphatic, aromatic, heterocyclic and conjugated aldehydes afforded the desired products in high yields. The method worked very well for acid sensitive aldehydes, such as furfural and also for enolizable aldehyde (entries c, d).



1 **4** **2** **5**

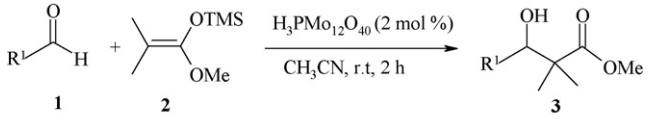
	R^1	R^2	5 %	TON[a]	TOF[b]
a	Phenyl	Phenyl	95	4750	2375
b	4-Cl-Phenyl	Phenyl	98	4900	2450
c	i-Propyl	Phenyl	88	4400	2200
d	c-Hexyl	Phenyl	96	4800	2400
e	2-Furyl	Phenyl	96	4800	2400
f	4-Pyridyl	Phenyl	95	4750	4750
g	Cinnamyl	Phenyl	90	4500	2250
h	Phenyl	Benzyl	88	3750	1875
i	Cinnamyl	Benzyl	85	3500	1750

[a] Turnover number (number of molecules converted per mol of PMo)
[b] Turnover frequency (turnover number per hour)

Scheme 1. .

Table 2
Reaction of benzaldehyde (**1a**), aniline (**4a**) with ketene silyl acetal (**2**) in the presence of different catalysts

Entry	Catalyst [Ref.]	Catalyst load (%)	Time (h)	Solvent	Yield
1	Sulfated zirconia [30]	150wt	5	CH_3CN	99
2	$InCl_3$ [31]	20	24	H_2O	54
3	Bismuth triflate [32]	2	8	THF	67
4	Phosphonium salt [25]	7	21	CH_2Cl_2	67
5	FeI_2 [24]	10	3	CH_2Cl_2	92
6	TMSOTf [23]	0.1	15	CH_2Cl_2	78
7	$TiCl_4$ [22]	100	1	CH_2Cl_2	85
8	$H_3PMo_{12}O_{40}$	2	2	CH_3CN	95



1 2 3

	R^1	3 %	TON[a]	TOF[b]
a	Phenyl	85	4250	2125
b	4-Cl-Phenyl	86	4300	2150
c	*i*-Propyl	90	4500	2250
d	*c*-Hexyl	90	4500	2250
e	2-Furyl	70	3500	1750
f	4-Pyridyl	80	4000	2000
g	Cinnamyl	75	3750	1875

[a] Turnover number (number of molecules converted per mol of PMo)
[b] Turnover frequency (turnover number per hour)

Scheme 2. .

In all cases, no undesired side products, such as Mukaiyama aldol are obtained under these conditions. We believe that this is mainly due to the rapid formation and activation of the imines catalyzed by PMo. Although the amount of catalyst has been optimized to 2 mol%, lesser amounts (1 mol%) also worked with longer reaction times.

In Table 2, we have compared the catalytic activity of PMo for the reaction of benzaldehyde and aniline with keten silyl acetal with those reported for other catalysts. It was observed that the reaction was more efficient in the presence of PMo when compared to the literature procedure [22–25,29–32].

As PMo is not soluble in AN, no PMo leaching as well as no contribution of homogeneous catalysis in the course of reaction was expected. To prove this, after 3 h, the catalyst was removed from AN by filtration and the supernatant was tested for activity. No activity was observed, indicating that there was no contribution of homogeneous catalysis in this reaction. No detectable amount of Mo and P was found in the supernatant by atomic absorption analysis. After reaction, the catalyst can be easily separated (by filtration) and reused after washing with dichloromethane with gradual decrease in its activity. For example, the reaction of benzaldehyde (**1a**), aniline (**4**) and ketene silyl acetal (**2**) afforded the corresponding β-amino ester in 95, 93 and 90% isolated yield over three cycles. The Keggin structure of the catalyst remains unchanged in these runs which proved by FTIR of the catalyst before and after use.

3. Conclusions

In summary, the synthesis of β-hydroxy esters and β-amino esters from aldehydes has been achieved by using PMo catalysis. This new protocol represents a safer, simpler and more environmentally friendly alternative to the classical conditions, avoiding the use of expensive and toxic bases or Lewis acids and therefore permitting the use of substrates sensitive to Lewis acid conditions. Further synthetic reactions using HPAs are now in progress.

4. Experimental section

4.1. General procedure I: preparation of β-hydroxy ester derivatives.

To a suspension containing $H_3PMo_{12}O_{40}$ (73 mg, 2 mol%) in reagent grade AN (4 mL) and aldehyde (2 mmol) was added and the mixture vigorously stirred for 10 min at room temperature. After, ketene silyl acetal (**2**) (350 mg, 2 mmol) was added, the mixture was stirred for additional 2 h. Dichloromethane (5 mL) was added to the mixture and the solid PMo was filtered and washed the solid residue with CH_2Cl_2 (5 mL). The filtrate was evaporated on a rotary evaporator and the crude product was purified by a short column chromatography on silica gel (eluted with ethyl acetate/hexane 2:1) to afford the pure product(s) in 70–92% yields (Scheme 2).

4.2. General procedure II: preparation of β-amino ester derivatives.

To a suspension consisting of reagent grade AN (4 mL), aldehyde (2 mmol) and amine (2.2 mmol) was added $H_3PMo_{12}O_{40}$ (73 mg, 2 mol%) and the mixture vigorously stirred for 10 min at room temperature. ketene silyl acetal (**2**) (350 mg, 2 mmol) was added and the mixture was stirred for an additional 2 h. Dichloromethane (5 mL) was added to the mixture and the solid PMo was filtered and washed the solid residue with CH_2Cl_2 (5 mL). The combined organic were concentrated under vacuum and the crude mixture was purified by column chromatography on silica gel (hexane:ethyl acetate, 2:1) to afforded pure products.

^{1}H-NMR, ^{13}C-NMR, IR were entirely consistent with the assigned structures. Spectroscopic data for selected examples follow: **3a:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.15 (s, 3H), 3.38 (brs, OH), 3.73 (s, 3H), 4.89 (s, 1H), 7.2–7.7 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): 19.5, 23.1, 48.1, 52.5, 78.3, 126.4, 127.3, 129.1, 141.3, 176.3; **3b:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (s, 3H), 1.14 (s, 3H), 3.41 (brs, OH), 3.71 (s, 3H), 4.89 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 19.5, 23.1, 48.1, 52.5, 78.3, 129.4, 131.3, 135.1, 141.3, 178.3; **3c:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (d, J = 7 Hz, 6H), 1.21 (s, 3H), 1.30 (s, 3H), 1.29 (m, 1H), 2.16 (brs, OH), 3.41 (d, J = 5 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 17.5, 21.1, 23.7, 24.2, 31.3, 46.7, 51.3,, 80.1, 178.1; **3d:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12–1.9 (m, 17H), 2.27 (m, 1H), 3.55 (d, J = 6.5 Hz, 1H) 3.65 (brs, OH), 3.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 16.5, 22.1, 22.7, 24.1, 30.3, 46.3, 52.3, 53.8, 82.1, 179.1; **3e:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (s, 3H), 1.25 (s, 3H), 3.45 (brs, OH), 3.63 (s, 3H), 4.52 (s, 1H), 6.01-6.12 (m, 2H), 7.2 (d, J = 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 20.6, 21.3, 47.0, 52.7, 79.1, 112.4, 115.3, 143.3, 151.8, 176.8; **3f:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (s, 3H), 1.16 (s, 3H), 3.76 (brs, OH), 3.71 (s, 3H), 4.99 (s, 1H), 7.24 (d, J = 5.5 Hz, 2H), 8.57 (d, J = 5.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 20.1, 22.1, 48.8, 52.1, 79.3, 120.4, 145.3, 148.3, 176.8; **3g**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (s, 3H), 1.25 (s, 3H), 3.61 (brs, OH), 3.74 (s, 3H), 4.70 (d, J = 4.5 Hz, 1H), 6.14–6.16 (m, 1H), 6.7 (d, J = 7.81 Hz, 1H), 7.30–7.59 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): 23.7, 24.3, 47.7, 52.3, 81.8, 126.9, 127.3, 128.2, 129.1, 133.7, 137.8, 169.7; **5b:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (s, 3H), 1.38 (s, 3H), 3.69 (s, 3H), 4.11 (brs, NH), 4.56 (s, 1H), 6.80 (d, J = 8.5 Hz, 2H), 7.11–7.41 (m, 5H), 7.84 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 24.1, 24.9, 47.1, 52.7, 64.4, 113.1, 115.6, 128.3, 129.8, 130.5, 130.7, 138.1, 146.3, 176.8;

5d: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12–1.9 (m, 16H), 2.27 (m, 1H), 3.56 (brs, NH), 3.71 (s, 3H), 4.13 (d, J = 10 Hz, 1H), 6.6–6.8 (m, 3H), 7.1–7.3 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 16.5, 22.1, 22.7, 24.1, 30.3, 36.3, 38.3, 51.8, 62.1, 113.1, 117.6, 127.4, 146.8, 179.1; **5e:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (s, 3H), 1.36 (s, 3H), 3.72 (s, 3H), 4.51 (brs, NH), 4.76 (s, 1H), 6.80–7.11 (m, 3H), 7.14-7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): 21.6, 23.9, 47.6, 52.5, 59.1, 108.3, 110.5, 114.2, 118.5, 129.5, 142.1, 147.3, 153.8, 177.1; **5g:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (s, 3H), 1.43 (s, 3H), 3.77 (s, 3H), 4.27 (brs, NH), 4.25 (d, J = 7.5 Hz, 1H), 6.14–6.16 (m, 1H), 6.7 (d, J = 7.81 Hz, 1H),6.7–7.2 (m, 5H), 7.30–7.59 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): 22.1, 24.1, 47.5, 52.4, 63.1,114.1, 118.1, 126.9, 127.3, 128.2, 128.9, 129.1, 133.7, 137.8, 147.9, 169.7; **5h:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (s, 3H), 1.36 (s, 3H), 3.7 (s, 3H), 4.61(s, 1H), 4.94 (s, 2H), 5.34 (brs, NH), 7.11–7.46 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): 24.1, 24.9, 47.1, 52.7, 55.3, 68.4, 113.1, 115.6, 128.3, 129.8, 130.5, 130.7, 138.1, 141.3, 176.8.

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