

Phosphomolybdic Acid: An Efficient and Reusable Catalyst for the Synthesis of β -Phosphono Malonates

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Phosphomolybdic acid ($\text{H}_3\text{PMo}_{12}\text{O}_{40}$) is an efficient and reusable catalyst for the synthesis of the phospho-Michael addition of phosphite esters with different types of α,β -unsaturated malonates to produce a variety of β -phosphono malonates.

Keywords: β -Phosphono malonates, Heteropoly acid, Phospho-Michael addition, Phosphite esters, Malonates

INTRODUCTION

Synthesis of phosphonate derivatives has considerably attracted the attention of organic chemists due to their wide range of applications in agriculture and bio-chemistry. For example, phosphonate derivatives are used as insecticides, herbicides, fungicides and plant-growth regulators in the area of agricultural chemistry [1]. They play an important role in our lives as antiviral agents and in mammalian cells as inhibitors of gene expression. They also play an important role in the treatment of bone disorders and in medical decalcification [2-4].

Direct phosphorus-carbon bond formation represents one of the most versatile and powerful tools for the synthesis of phosphonates. Amongst these methods, phospho-Michael addition, that is, the addition of a phosphorous nucleophile to an electron-deficient alkene has received remarkable attention from organic chemists [5,6]. These reactions are most commonly promoted by bases [5-9], acids [10,11], microwaves [12], transition metals [13,14] or radical initiators such as AIBN [15,16]. Although these methods are valuable, they suffer from one or more of the following disadvantages:

high temperature; long reaction times; low yields; tedious work-up protocols; requiring a promoter such as microwave and using large amounts of un-recyclable catalyst which would eventually result in the generation of a large amount of toxic waste. Hence, the development of a new and efficient catalyst for this important transformation is still in demand.

For the last two decades, the use of heteropoly acids as environmentally benign catalysts has become important in industries related with fine chemicals [17]. Heteropoly acids, especially those comprising the strongest Keggin-type structure such as $\text{H}_3\text{PW}_{12}\text{O}_{40}$, $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ and $\text{H}_4\text{SiW}_{12}\text{O}_{40}$, are more active catalysts than the conventional inorganic and organic acids [17-20]. In addition, solid heteropoly acids are soluble in water and polar organic solvents such as lower alcohols and carboxylic acids, but insoluble in hydrocarbons [21]. These properties make it possible to recover heteropoly acids from the reaction mixture without neutralization, simply by extracting with H_2O or precipitating by a hydrocarbon solvent [21].

Recently, we have focused our efforts on the development of useful and novel methods for the synthesis of phosphonate derivatives [22-31]. In this connection, herein, we report the successful synthesis of β -phosphono malonates *via* phospho-Michael addition of trialkyl phosphites to α,β -unsaturated

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malonates catalyzed by heteropoly acids as recyclable catalysts.

EXPRIMENTAL

Chemicals and Apparatus

Chemicals were purchased from Merck and Fluka Chemical Companies. All of the products were identified by their physical and spectral data. NMR spectra were recorded in ppm in CDCl₃ on a Bruker Avance DPX-250 instrument using TMS as internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP5050A. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV₂₅₄ plates.

General Procedure for the Synthesis of β -Phosphono Malonates (2a-o)

H₃PMo₁₂O₄₀ (0.02 mmol) was added to a stirring mixture of α,β -unsaturated malonates (1a-o) (1 mmol) and P(OEt)₃ (1 mmol) at ambient temperature or at 80 °C (Table 2). The reaction mixture was stirred for the appropriate time (Table 2). *n*-Hexane was added to the reaction mixture. The catalyst was separated from the resulting mixture by filtration and washed with *n*-hexane (2 × 10 ml). Evaporation of the solvent of the filtrate under reduced pressure gave the crude products. The pure products were isolated by chromatography on silica gel eluted with *n*-hexane:EtOAc (1:1).

Spectral Data for Selected Product

[1-Phenyl-2,2-dicyanoethyl] phosphonic acid diethyl ester (2a). ¹H NMR (CDCl₃, TMS): δ 1.11 (t, 3H, ³J_{HH} = 6.8 Hz), 1.33 (t, 3H, ³J_{HH} = 7.0 Hz), 3.65 (dd, 1H, ³J_{HH} = 8.0, ²J_{HP} = 21.0 Hz), 3.91-4.21 (m, 4H), 4.55 (t, 1H, ³J_{HH} = 8.3 Hz), 7.43 (s, 5H) ppm; ¹³C NMR (CDCl₃, TMS): δ 16.1 (d, ³J_{CP} = 5.6 Hz), 16.2 (d, ³J_{CP} = 5.6 Hz), 25.5, 44.6 (d, ¹J_{CP} = 144.0 Hz), 63.4 (d, ²J_{CP} = 7.5 Hz), 64.4 (d, ²J_{CP} = 7.0 Hz), 111.1 (d, ³J_{CP} = 12.5 Hz), 111.3 (d, ³J_{CP} = 10.0 Hz), 129.2, 129.3, 129.4, 129.8 ppm; ³¹P NMR (CDCl₃, TMS): δ 20.04 ppm; MS (70 eV), m/e: 292 (M⁺), 155 [M⁺-P(O)(OEt)₂].

[1-(2-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (2b). ¹H NMR (CDCl₃, TMS): δ 1.11 (t, 3H, ³J_{HH} = 7.0 Hz), 1.36 (t, 3H, ³J_{HH} = 7.0 Hz), 3.75-4.30 (m, 4H),

4.46 (dd, 1H, ³J_{HH} = 8.2, ²J_{HP} = 21.2 Hz), 4.61 (t, 1H, ³J_{HH} = 8.5 Hz), 7.35 (d, 2H, ³J_{HH} = 4 Hz), 7.47 (s, 1H), 7.75 (d, 1H, ³J_{HH} = 5.3 Hz) ppm; ¹³C NMR (CDCl₃, TMS): δ 16.0 (d, ³J_{CP} = 6.3 Hz), 16.2 (d, ³J_{CP} = 5.6 Hz), 24.9, 39.4 (d, ¹J_{CP} = 144.6 Hz), 63.6 (d, ²J_{CP} = 7.5 Hz), 64.4 (d, ²J_{CP} = 6.9 Hz), 110.9 (d, ³J_{CP} = 5.6 Hz), 111.1, 127.8, 128.6, 129.6, 130.6, 135.1 ppm; ³¹P NMR (CDCl₃, TMS): δ 19.47 ppm; MS (70 eV), m/e: 326 (M⁺), 328 (M⁺+2), 189 [M⁺-P(O)(OEt)₂], 191 [(M⁺+2)-P(O)(OEt)₂].

[1-(4-Chlorophenyl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (2c). ¹H NMR (CDCl₃, TMS): δ 1.16 (t, 3H, ³J_{HH} = 7.0 Hz), 1.33 (t, 3H, ³J_{HH} = 7.0 Hz), 3.62 (dd, 1H, ³J_{HH} = 7.5 Hz, ²J_{HP} = 21.5 Hz), 3.82-4.19 (m, 4H), 4.55 (t, 1H, ³J_{HH} = 7.7 Hz), 7.42 (s, 4H) ppm; ¹³C NMR (CDCl₃, TMS): δ 16.1 (d, ³J_{CP} = 5.0 Hz), 16.2 (d, ³J_{CP} = 5.6 Hz), 25.5, 43.9 (d, ¹J_{CP} = 144.7 Hz), 63.5 (d, ²J_{CP} = 7.0 Hz), 64.4 (d, ²J_{CP} = 7.0 Hz), 111.0 (d, ³J_{CP} = 11.9 Hz), 111.2 (d, ³J_{CP} = 11.3 Hz), 128.8, 129.6, 130.7, 135.7 ppm; ³¹P NMR (CDCl₃, TMS): δ 19.42 ppm; MS (70 eV), m/e: 326 (M⁺), 328 (M⁺+2), 189 [M⁺-P(O)(OEt)₂], 191 [(M⁺+2)-P(O)(OEt)₂].

[1-(Naphthalen-2-yl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (2h). ¹H NMR (CDCl₃, TMS): δ 1.08 (t, 3H, ³J_{HH} = 7.0 Hz), 1.36 (t, 3H, ³J_{HH} = 7.0 Hz), 3.65-4.22 (m, 5H), 4.66 (t, 1H, ³J_{HH} = 8.5 Hz), 7.52-7.58 (m, 3H), 7.87-7.96 (m, 4H) ppm; ¹³C NMR (CDCl₃, TMS): δ 16.1 (d, ³J_{CP} = 5.6 Hz), 16.2 (d, ³J_{CP} = 6.2 Hz), 25.7, 44.8 (d, ¹J_{CP} = 144.0 Hz), 63.4 (d, ²J_{CP} = 7.5 Hz), 64.4 (d, ²J_{CP} = 7.0 Hz), 111.2 (d, ³J_{CP} = 13.2 Hz), 111.3 (d, ³J_{CP} = 8.2 Hz), 125.9, 126.9, 127.2, 127.6, 127.7, 127.8, 128.2, 129.2, 129.4, 133.3 ppm; ³¹P NMR (CDCl₃, TMS): δ 19.95 ppm.

[1-(Furan-2-yl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (2i). ¹H NMR (CDCl₃, TMS): δ 1.24-1.37 (m, 6H), 3.87 (dd, 1H, ²J_{HH} = 6.5 Hz, ²J_{HP} = 22.7 Hz), 3.98-4.23 (m, 4H), 4.51 (t, 1H, ²J_{HH} = 8.7 Hz), 6.44 (s, 1H), 6.62 (s, 1H), 7.49 (s, 1H) ppm; ¹³C NMR (CDCl₃, TMS): δ 16.1, 16.2, 24.3, 39.1 (d, ¹J_{CP} = 147.1 Hz), 63.9 (d, ²J_{CP} = 6.9 Hz), 64.2 (d, ²J_{CP} = 6.9 Hz), 110.9 (d, ³J_{CP} = 9.4 Hz), 111.1 (d, ³J_{CP} = 11.9 Hz), 111.3, 111.7, 143.2, 144.0 ppm; ³¹P NMR (CDCl₃, TMS): δ 19.88 ppm; MS (70 eV), m/e: 282 (M⁺), 145 [M⁺-P(O)(OEt)₂].

[1-(Pyridin-3-yl)-2,2-dicyanoethyl] phosphonic acid diethyl ester (2k). ¹H NMR (CDCl₃, TMS): δ 1.18 (t, 3H, ³J_{HH} = 6.8 Hz), 1.33 (t, 3H, ³J_{HH} = 7.0 Hz), 3.65 (dd, 1H, ³J_{HH} =

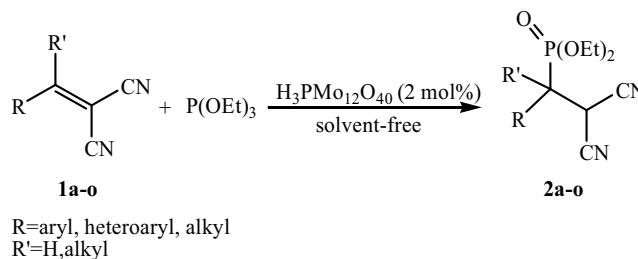
6.8 Hz, $^2J_{\text{HP}} = 21.6$ Hz), 3.92-4.21 (m, 4H), 4.63 (t, 1H, $^3J_{\text{HH}} = 8.5$ Hz), 7.39 (t, 1H, $^3J_{\text{HH}} = 6.5$ Hz), 7.95 (d, 1H, $^3J_{\text{HH}} = 6.5$ Hz), 8.67 (s, 2H) ppm; ^{13}C NMR (CDCl_3 , TMS): δ 16.1 (d, $^3J_{\text{CP}} = 5.0$ Hz), 16.2 (d, $^3J_{\text{CP}} = 5.0$ Hz), 25.3, 42.1 (d, $^1J_{\text{CP}} = 144.6$ Hz), 63.8 (d, $^2J_{\text{CP}} = 7.0$ Hz), 64.5 (d, $^2J_{\text{CP}} = 7.0$ Hz), 110.8 (d, $^3J_{\text{CP}} = 10.7$ Hz), 111.0 (d, $^3J_{\text{CP}} = 11.9$ Hz), 124.0, 126.7, 136.5, 150.5, 150.8 ppm; ^{31}P NMR (CDCl_3 , TMS): δ 19.03 ppm; MS (70 eV), m/e: 293 (M^+), 156 [$\text{M}^+ - \text{P}(\text{O})(\text{OEt})_2$].

1,1-Dicyanopentane-2-yl phosphonic acid diethyl ester (2l). ^1H NMR (CDCl_3 , TMS): δ = 1.00 (t, 3H, $^3J_{\text{HH}} = 7.0$ Hz), 1.37 (t, 6H, $^3J_{\text{HH}} = 7.0$ Hz), 1.61 (q, 2H, $^3J_{\text{HH}} = 7.0$ Hz), 1.73-2.10 (m, 2H), 2.29-2.34 (m, 1H), 4.16-4.25 (m, 4H), 4.29-4.35 (m, 1H). ^{13}C NMR (CDCl_3 , TMS): δ = 13.73, 16.3 (d, $^3J_{\text{CP}} = 5.6$ Hz), 20.7 (d, $^3J_{\text{CP}} = 7.6$ Hz), 29.2, 37.8 (d, $^1J_{\text{CP}} = 144.9$ Hz), 110.7 (d, $^3J_{\text{CP}} = 5.0$ Hz), 112.2 (d, $^3J_{\text{CP}} = 17.0$ Hz). MS (70 eV): 259 ($\text{M}^+ + 1$), 121 [$\text{M}^+ - \text{P}(\text{O})(\text{OEt})_2$].

RESULTS AND DISCUSSIONS

At first, the ability of some heteropoly acids such as $\text{H}_3\text{PMo}_{12}\text{O}_{40}$, $\text{H}_3\text{PW}_{12}\text{O}_{40}$, $\text{H}_4\text{SiW}_{12}\text{O}_{40}$ and $(\text{NH}_4)_3\text{PMo}_{12}\text{O}_{40}$ in the phospho-Michael addition of triethyl phosphite with benzylidenemalonitrile (**1a**) under solvent-free conditions at room temperature was investigated (Table 1). Amongst heteropoly acids tested, $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ turned out to be the most effective catalyst in terms of yield and reaction time (Table 1, entry 1). In order to show the role of the catalyst, a similar reaction in the absence of the catalyst was triggered. This reaction led to the formation of the desired product (**2a**) in low yield after 24 h (Table 1, entry 5), which was a good indication of the crucial role of the catalyst in the reaction.

Then, the reaction of various structurally diverse α,β -



Scheme 1

unsaturated malonates with triethyl phosphite were examined in the presence of $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ to show the generality and scope of the method (Scheme 1). The results of these studies are summarized in Table 2.

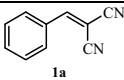
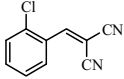
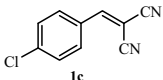
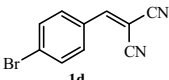
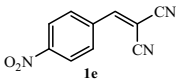
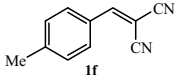
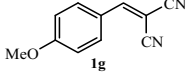
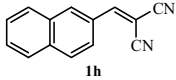
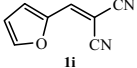
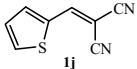
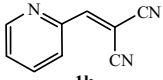
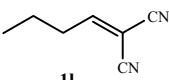
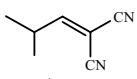
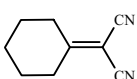
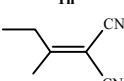
As it is obvious from Table 2, the catalytic phospho-Michael addition of triethyl phosphite with benzylidenemalonitriles containing different electron-donating and electron-withdrawing groups proceeded well and the desired products (**2a-g**) were obtained in good to high yields (entries 1-7). In the reaction of **1b-d** and **1g**, the catalyst was compatible with functional groups such as Cl, Br and O-Me. No competitive nucleophilic methyl ether cleavage was observed for the substrate possessing an aryl-O-Me group (entry 7), despite the strong nucleophilicity of phosphites. α,β -Unsaturated malonates substituted with polyaromatic and heteroaromatic groups underwent successful phospho-Michael addition by triethyl phosphite (entries 8-11). This method is also applicable for the synthesis of β -phosphono malonates from the reaction of triethyl phosphite with α,β -unsaturated malonates substituted with aliphatic groups (**1l** and **1m**). Similar reactions with β,β -disubstituted malonates (**1n** and **1o**) led to the formation of the desired product in good yields

Table 1. Phospho-Michael Addition of Triethyl Phosphite to **1a** Catalyzed by HPAs

Entry	Catalyst	Time (h)	Yield (%) ^a
1	$\text{H}_3\text{PMo}_{12}\text{O}_{40}$	0.25	88
2	$\text{H}_3\text{PW}_{12}\text{O}_{40}$	1	85
3	$\text{H}_4\text{SiW}_{12}\text{O}_{40}$	2	50
4	$(\text{NH}_4)_3\text{PMo}_{12}\text{O}_{40}$	3	89
5	-	24	50

^aIsolated yield; Conditions: **1a**/phosphite/catalyst:1/1/0.02, room temperature, solvent-free.

Table 2. Synthesis of β -Phosphono Malonates Catalyzed by $\text{H}_3\text{PMo}_{12}\text{O}_{40}$

Entry	Substrate	Product	Time (min)	Yield (%) ^a
1	 1a	2a	15	88
2	 1b	2b	5	82
3	 1c	2c	30	95
4	 1d	2d	15	85
5	 1e	2e	5	83
6	 1f	2f	60	85
7	 1g	2g	30	84
8	 1h	2h	5	80
9	 1i	2i	5	85
10	 1j	2j	30	86
11	 1k	2k	5	98
12	 1l	2l	4 h ^b	72
13	 1m	2m	4 h ^b	64
14	 1n	2n	2 h ^b	70
15	 1o	2o	4 h ^b	71

^aIsolated yield; Conditions: α,β -unsaturated malonate/phosphite/catalyst: 1/1/0.02. All the products were characterized by spectroscopic methods and compared with the authentic spectra [32,33]. ^bReaction temperature = 80 °C.

(entries 14 and 15).

The possibility of recycling the catalyst was examined using the reaction of benzylidenemalonitrile (**1a**) and triethyl phosphite under solvent-free conditions at room temperature. Upon completion of the reaction, *n*-hexane was added to the reaction mixture. Then the catalyst was separated by a simple filtration from the resulting heterogeneous mixture, washed with *n*-hexane (3 × 30 ml), dried and reused for subsequent runs. The recycled catalyst was reused five times without any additional treatment. The average isolated yield of **2a** for five consecutive runs was 85%, which clearly demonstrates the practical reusability of this catalyst (Fig. 1).

Finally, we have evaluated the generality of the present method for the phospho-Michael addition of different phosphite esters with benzylidenemalonitrile (**1a**). The results of these studies are summarized in Table 3.

As it is shown in Table 3, **1a** underwent catalytic phospho-Michael addition with trimethyl/tri-*iso*-propyl phosphite and the desired products were obtained in good yields (entries 1 and 2). A similar reaction in the presence of triphenyl phosphite as a phosphorus nucleophile led to the formation of the desired product in low yield (entry 3). No yield was obtained when the reaction took place out in the presence of diethyl phosphite.

CONCLUSIONS

H₃PMo₁₂O₄₀ was found to be an efficient and reusable catalyst for the synthesis of a variety of β-phosphono malonates by phospho-Michael addition of phosphite esters with different α,β-unsaturated malonates. Short reaction times,

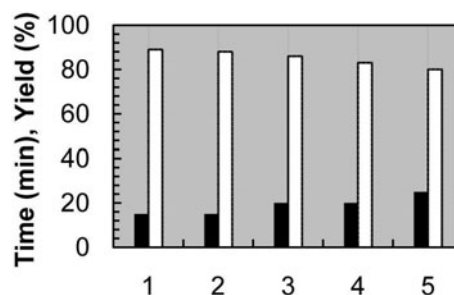


Fig. 1. Reusability of H₃PMo₁₂O₄₀ as a catalyst for the synthesis of β-phosphono malonate **2a**: (■) time, (□) yield.

simple work-up, ease of catalyst recovery, no by-product formation and using a catalytic amount of H₃PMo₁₂O₄₀ make this method attractive and a useful addition to the presently existing methodologies.

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Table 3. Phospha-Michael Addition of Various Phosphite Esters to **1a** Catalyzed by H₃PMo₁₂O₄₀

Entry	Phosphite	Time (h)	Yield (%) ^a
1 ^b	P(OMe) ₃	2	73
2 ^b	P(O- <i>i</i> -Pr) ₃	1	78
3	P(OPh) ₃	3	15
4	HP(O)(OEt) ₂	24	0

^aIsolated yield; Conditions: **1a**/phosphite/catalyst:1/1/0.02, room temperature, (except for entries 1 and 2), solvent-free. ^bReaction temperature = 50 °C.

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