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ARTICLE

One-Pot Four-Component Dakin-West Synthesis of β-Acetamido Ketones Catalyzed by a Vanadium-Substituted Heteropolyacid

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Abstract: The multicomponent condensation of an aryl aldehyde, acetyl chloride, acetonitrile, and enolizable ketone as one-pot synthesis of β-acetamido ketones in high yields was investigated using commercial, non-corrosive, and environmentally benign Keggin and Wells-Dawson heteropolyacid catalysts. The best catalyst was $H_5PW_{10}V_2O_{40}$. The methodology used simple experimental conditions, and the short reaction times and high yields indicate it is a useful strategy for the large scale synthesis of β-acetamido ketones.

Key words: homogeneous catalysis; heteropolyacid; Keggin; Wells-Dawson; Dakin-West; β-acetamido ketone

Acetamido ketone derivatives are versatile intermediates in the synthesis of important biological and pharmacological organic compounds such as the natural nucleoside antibiotics nikkomycins, neopolyoxins, and several antibiotic drugs [1–4]. The best known route for the synthesis of these important compounds is the Dakin-West reaction [5,6]. A simple and direct method for the synthesis of a β-acetamido ketone was reported by Bhatia et al. [7] in 1994, which involved the one-pot multicomponent coupling condensation of an enolizable ketone, aldehyde, and acetonitrile in the presence of acetyl chloride.

Synthetic strategies based on one-pot multicomponent reactions have emerged as an efficient and powerful tool in synthetic organic chemistry, especially in drug discovery processes [8]. In the last decade, multicomponent synthetic procedures have been considered for a broad range of synthetic routes [9–11]. These efficient and economic reactions have even been used with pharmacologically relevant templates for combinatorial and parallel synthesis [12,13]. Multicomponent reactions allow more than two building blocks to be combined in a practical, time-saving one-pot operation, and give complex structures by the simultaneous formation of two or more bonds [14].

Earlier reports on the synthesis of β-acetamido ketones through multicomponent reactions used catalysts such as $CoCl_2$ [15], montmorillonite K10 clay [16], $BiCl_3$ [17], silica sulfuric acid [18], transition metal and main group triflates, BF_3, $CuCl_2$, $BiCl_3$, $LaCl_3$, $LiClO_4$, $InCl_3$ [19], heteropolyacids [20], and solid acid Hβ-zeolite [21]. Although these methods are valuable, most of them suffer from one or more of the disadvantages of employing expensive catalysts, high temperature, long reaction times or harsh reaction conditions, and tedious work up. Hence, the development of new catalysts with more efficiency is still in demand. The designing of new catalysts and exploring their catalytic activities have profound effects in the efficiency of a wide range of organic syntheses and more economical and environmentally friendly chemistry [22,23]. Here, we developed strong super-acidic vanadium (V)-substituted Keggin and Wells-Dawson heteropolyacids, notably $H_5PW_{10}V_2O_{40}$, as catalysts for the efficient and facile synthesis of β-acetamido ketones through the one-pot condensation of an aryl aldehyde, acetophenone, acetyl chloride, and acetonitrile (Scheme 1).

1 Experimental

1.1 Preparation of heteropolyacids

1.1.1 Preparation of 10-molybdo-2- vanadophosphoric-acid $H_5PMo_{10}V_2O_{40}\cdot 34H_2O$ [24,25]

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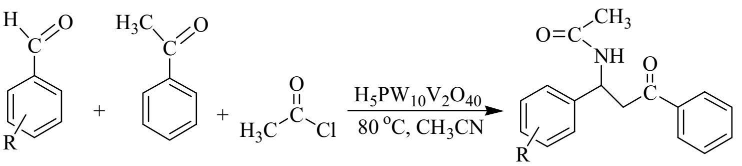


Scheme 1. Synthesis of β-acetamido ketones through one-pot condensation of an aryl aldehyde, acetophenone, acetyl chloride, and acetonitrile.

Sodium metavanadate (12.2 g, 100 mmol) was dissolved by boiling in 50 ml of water and then mixed with Na_2HPO_4 (3.55 g, 25 mmol) in 50 ml water. After the solution was cooled, 5 ml (17 mol/L, 85 mmol) of concentrated sulfuric acid was added until the solution developed a red color. Then, 60.5 g (250 mmol) of $Na_2MoO_4\cdot 32H_2O$ was dissolved in 100 ml of water and added to the red solution with vigorous stirring, followed by the slow addition of concentrated sulfuric acid (42 ml, 17 mol/L, 714 mmol). The hot solution was allowed to cool at room temperature. The 10-molybdo-2-vanadophosphoricacid was extracted with 500 ml of diethyl ether. Air was passed through the heteropoly etherate (bottom layer) to free it from ether. The remaining solid residue was dissolved in water and then allowed to crystallize. The large red crystals formed were filtered, washed with water, and air-dried. The characterization data, calcd (observed), were: P, 1.32 (1.37); Mo, 40.82 (40.61); V, 4.33 (4.40); H_2O, 26.05 (26.18). FT-IR (KBr, cm^{-1}): 1060 (s), 962 (vs), 915 (sh), 870 (m), 770 (vs).

1.1.2 Preparation of 10-tungsto-2-vanadophosphoricacid $H_5PW_{10}V_2O_{40}\cdot 30H_2O$ [25,26]

Sodium metavanadate ($NaVO_3$, 12.2 g, 100 mmol) was dissolved in 50 ml of boiling water and mixed with a 50 ml aqueous solution of di-sodium hydrogen phosphate (Na_2HPO_4, 3.55g, 25 mmol). After the resulting solution was cooled to room temperature, concentrated sulfuric acid (5 ml, 17 mol/L, 85 mmol) was added to give a red solution. Then, 100 ml aqueous solution of sodium tungstate dihydrate ($Na_2WO_4\cdot 2H_2O$, 82.5 g, 250 mmol) was added to the red solution with vigorous stirring, followed by the slow addition of concentrated sulfuric acid (42 ml, 17 mol/L, 714 mmol). Extraction of the solution with diethyl ether (500 ml) followed by evaporation in air afforded orange-red crystals of $H_5PW_{10}V_2O_{40}$ (yield, 74%). The characterization data, calcd (observed), were: P, 0.98 (1.05); W, 58.24 (58.12); V, 3.22 (3.16); H_2O, 17.12 (17.26). FT-IR (KBr, cm^{-1}): 1070 (s), 980 (vs), 885 (s), 788 (vs).

1.1.3 Preparation of potassium 9-tungsto-2-molybdo-1-vanadosilicate $K_5[\alpha\text{-}SiMo_2VW_9O_{40}]\cdot 10H_2O$ [27]

Sodium vanadate (4.8 g, 40 mmol) was dissolved in 230 ml of water. This solution was acidified by 4 mol/L HCl (45 ml). Solid $K_8SiMo_2W_9O_{39}\cdot 20H_2O$ (120 g, 40 mmol) was slowly added to the vigorously stirred solution. The desired yellow potassium salt was precipitated by the addition of solid potassium chloride (50 g). The product was filtered off, washed with saturated potassium chloride solution, and air dried (yield = 100 g (84%)). The characterization data, calcd (observed), were: K, 6.45 (6.27); Si, 0.93 (1.08); Mo, 6.33 (6.12); V, 1.68 (1.76); W, 54.58 (54.40); H_2O, 8.90 (9.01). FT-IR (KBr, cm^{-1}): 1007 (w), 960 (m), 912 (s), 874 (sh), 770 (vs).

1.1.4 Preparation of potassium 9-tungsto-3-vanadosilicate $K_7[\alpha\text{-}SiV_3W_9O_{40}]\cdot 10H_2O$ [27]

Sodium vanadate (1.9 g, 15.5 mmol) was dissolved in 300 ml of water. $Na_{10}[\alpha\text{-}SiW_9O_{34}]\cdot 18H_2O$ (145 g, 52 mmol) was added to the stirred solution, followed by the addition of 185 ml of 6 mol/L sulfuric acid. Then, the solution was maintained under stirring for 45 min. The pH was adjusted to be between 6 and 7 by the addition of solid potassium carbonate. An orange potassium salt (~100 g) was precipitated by the addition of solid potassium chloride (80 g) and re-crystallized in water. The characterization data, calcd (observed), were: K, 9.34 (9.12); Si, 0.96 (1.12); V, 5.16 (5.28); W, 56.48 (56.73); H_2O, 6.14 (6.32). FT-IR (KBr, cm^{-1}): 1004 (w), 960 (s), 900 (vs), 805 (vs), 740 (vs).

1.1.5 Preparation of potassium 9-tungsto-3-molybdo-silicate $K_4[\alpha\text{-}SiMo_3W_9O_{40}]\cdot 5H_2O$ [27]

Sodium molybdate (8 g, 33 mmol) was dissolved in 70 ml of water. A 30 ml portion of 4 M HCl was added to the stirred solution. $Na_{10}[\alpha\text{-}SiW_9O_{34}]\cdot 18H_2O$ (30 g, 10.8 mmol) was quickly added. The yellow potassium salt, $K_4[\alpha\text{-}SiMo_3W_9O_{40}]$, was precipitated by the addition of solid potassium chloride (14 g) to the stirred solution (yield = 25 g (80%). The characterization data, calcd (observed), were: K, 5.47 (5.63); Si, 1.01 (1.14); Mo, 10.07 (10.24); W, 57.89 (57.33); H_2O, 3.14 (3.23). FT-IR (KBr, cm^{-1}): 1012 (w), 958 (m), 918 (s), 888 (vw), 868 (vw), 775 (vs).

1.1.6 Preparation of the acids $H_{4+x}[\alpha\text{-}SiMo_{3-x}V_xW_9O_{40}]$ (x = 0, 1, 3) [27]

The potassium salt (15 g, 5 mmol) of each compound was dissolved in 65 ml of water and placed in a separatory funnel. Then, diethyl ether was added, followed by the slow addition of concentrated hydrochloric acid (55, 85, or 100 ml for $x = 0$, 1, or 3, respectively). The heavy phase was collected and diethyl ether was evaporated under vacuum. The resulting solid was dissolved in a minimum amount of water. Finally, the desired heteropolyacid was slowly crystallized at room temperature.

1.1.7 Preparation of Preyssler $K_{12}Na_2[NaP_5W_{30}O_{110}]$ and its acidic form $H_{14}[NaP_5W_{30}O_{110}]$ [28]

Ortho-phosphoric acid 90% (75 ml, 1.2 mol) was slowly added to 50 ml of an aqueous solution of $Na_2WO_4 \cdot 2H_2O$ (99 g, 0.3 mol) at 45 °C, and the resulting mixture was refluxed for 5 h. The solution obtained was diluted with 15 ml of water. Then, powdered KCl (22.5 g, 0.32 mol) was slowly added to the vigorously stirred solution over 35 min at room temperature. The pale green impure precipitate was filtered and washed with CH_3COOK (0.1 mol/L). The white needle-like crystals of potassium salt of the Preyssler's anion were re-crystallized from hot water. The free acid was prepared by passing a solution of 11.4 g potassium salt in 20 ml of water through a column (50 cm×1 cm) of Dowex 50WX8 in the H form. The evaporation of the eluent to dryness in vacuum resulted in $H_{14}[NaP_5W_{30}O_{110}]$. The characterization data for $K_{12}Na_2[NaP_5W_{30}O_{110}] \cdot 15H_2O$, calcd (observed), were: K, 5.69 (5.81); Na, 0.84 (0.71); P, 1.88 (1.74); W, 66.95 (66.83); H_2O, 3.28 (3.35). FT-IR (KBr, cm^{-1}): 1160 (s), 1070 (m), 1010 (w), 980 (vw), 920 (vs), 890 (vs), 760 (vs). The characterization data for $H_{14}[NaP_5W_{30}O_{110}] \cdot 58H_2O$, calcd (observed), were: Na, 0.27 (0.32); P, 1.82 (1.90); W, 64.8 (64.92); H_2O, 12.27 (12.40).

1.2 General procedure for the synthesis of β-acetamido ketones

A mixture of aromatic aldehyde (1 mmol), acetophenone (1 mmol), and acetyl chloride (2 mmol) in acetonitrile (4 ml) was treated with a catalytic amount of the desired heteropolyacid at 80 °C. The progress of the reaction was monitored by TLC. The work up procedure of this reaction was very simple. After completion of the reaction, the mixture was filtered to separate the catalyst. The solid crude product was washed with petroleum ether and filtered. The pure product was obtained, if needed, by re-crystallization from an ethanol-water mixture. Silica gel 60 (70–230 mesh) was used for column chromatography. Infrared spectra were run on a 8700 Shimadzu Fourier transform spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 200-MHz instrument using TMS as an internal reference. All products were identified by comparing their NMR and IR data with those reported in the literature. Spectral data for selected β-acetamido ketones [7,20,29] are listed as follows.

β-Acetamido-β-(phenyl)propiophenone. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.03 (s, 3H), 3.34 (dd, J = 6.6 and 9.7 Hz, 1H), 3.67 (dd, J = 6.6 and 9.7 Hz, 1H), 5.60 (m, 1H), 7.32 (s, 1H), 7.58 (d, J = 9.1 Hz, 5H), 7.76 (d, J = 9.1 Hz, 5H); IR (KBr, cm^{-1}): 3252, 3046, 1667, 1624, 1574, 1288, 1082, 878, 819.

β-Acetamido-β-(4-chlorophenyl)propiophenone. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.00 (s, 3H), 3.40 (dd, J = 6.9 and 9.9 Hz, 1H), 3.71 (dd, J = 6.9 and 9.9 Hz, 1H), 5.54 (m, 1H), 7.02 (m, 5H), 7.45 (m, 3H), 7.84 (d, J = 9.1 Hz, 2H); IR (KBr, cm^{-1}): 3265, 3082,1678, 1642, 1556, 1245, 1104, 887, 823, 683.

β-Acetamido-β-(3-nitrophenyl)propiophenone. ^1HNMR (200 MHz, $CDCl_3$): δ 1.87 (s, 3H), 3.11 (d, J = 15.9 Hz, 1H), 3.52 (d, J = 12.1 Hz, 1H), 5.50 (s, 1H), 7.30 (m, 5H), 7.80 (d, J = 6.2 Hz, 2H), 8.00 (d, J = 6.2 Hz, 2H); IR (KBr, cm^{-1}): 3290, 3024, 2245, 1680, 1649, 1542, 1440, 1215, 987, 750, 680, 545.

β-Acetamido-β-(2-hydroxyphenyl)propiophenone. ^1H NMR (200 MHz, $CDCl_3$): δ 2.00 (s, 3H), 3.49 (d, J = 7.2 Hz, 1H), 3.68 (d, J = 7.1 Hz, 1H), 6.87 (s, 1H), 7.50–7.72 (m, 5H), 7.95 (d, J = 5.9 Hz, 2H), 8.23 (d, J = 5.2 Hz, 2H); IR (KBr, cm^{-1}): 3286, 2845, 1679, 1638, 1595, 1501, 1446, 1341, 1289, 851, 747, 681, 588.

β-Acetamido-β-(4-nitrophenyl)propiophenone. ^1H NMR (200 MHz, $CDCl_3$): δ 2.01 (s, 3H, CH_3), 3.38 (dd, J = 5.6 and 17.4 Hz, 1H, CH_2), 3.85 (dd, J = 7.1 and 17.4 Hz, 1H, CH_2), 5.60 (m, 1H, methyne H), 7.19–7.54 (m,7H, Ar-H), 7.87 (d, J = 7.7 Hz, 2H, Ar-H), 9.18 (br, 1H, NH); IR (KBr, cm^{-1}): 3285,1682, 1648,1520,1350, 1300, 751.

β-Acetamido-β-(4-methoxyphenyl)propiophenone. ^1H NMR (200 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.47 (s, 3H), 3.51 (dd, J = 7.1 and 10.0 Hz, 1H), 3.84 (dd, J = 7.1 and 10.0 Hz, 1H), 5.58 (m, 1H), 7.39 (s, 1H), 7.52 (m, 5H), 7.96 (m, 4H); IR (KBr, cm^{-1}): 3263, 3051, 1672, 1630, 1581, 1290, 1081, 878, 817.

2 Results and discussion

2.1 Introducing the Keggin $H_5PW_{10}V_2O_{40}$ framework, effect of structure on reactivity

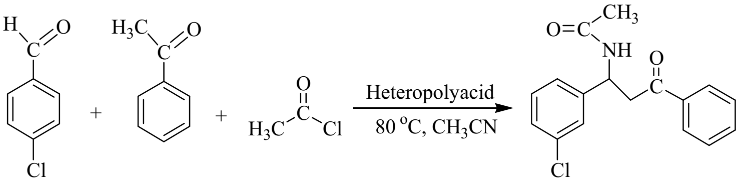
Phosphotungstic (molybdic) acids are well recognized effective catalysts in many acid catalyzed reactions. They consist of large anions whose structure is referred to as the primary structure. Several cations and water molecules form an arrangement with the anions to form the secondary structure [30]. The $[P(Mo,W)_{12}O_{40}]^{3-}$ anions have the well-known Keggin structure composed of a central tetrahedral PO_4 surrounded by 12 edge-sharing metal-oxygen MoO_6. Although other elements, such as silicon, can be used as the central atom, phosphorus has been the most preferred element and it leads to the most stable anion in the heteropoly compounds.

It is well recognized that a vanadyl cation can be added as a monovalent substituent in the heteropolyacid structure through the replacement of the protons [20]. Although, vanadium does not have an important effect on the structure of the acid, it strongly influences physicochemical properties such as hydration extent, redox and catalytic capability of the Keggin compound.

First, the catalytic efficiency of different heteropolyacids in the four-component condensation of *para*-chlorobenzaldehyde with acetophenone and acetyl chloride in refluxing acetonitril was studied (Table 1). Keggin $H_5PW_{10}V_2O_{40}$ and $H_5PMo_{10}V_2O_{40}$ were active catalysts due to their bifunctional nature originating from their strong acidic protons and the presence of the vanadium transition metal ion as an effective electron acceptor resource. $H_5PW_{10}V_2O_{40}$ gave the best catalytic activity and led to 88% conversion after 0.5 h, while the other heteropolyacids such as Keggin $H_3PW_{12}O_{40}$, V-containing silico(phospho)tungstic(molybdic)acids $H_7SiW_9V_3O_{40}$ and $H_5PMo_{10}V_2O_{40}$, and Wells-Dawson $H_6P_2W_{18}O_{62}$ showed comparable activity and produced 77%−86% yields in 3 h. These results demonstrated the higher catalytic efficiency of the vanadium-containing catalysts over the others. As shown in Table 1, the heteropolyacid catalysts without the vanadium component showed less efficiency.

Mixed metal substituted heteropolyacids such as Keggin $H_5SiW_9Mo_2VO_{40}$, Wells-Dawson $H_6P_2Mo_{18}O_{62}$, and Preyssler $H_{14}NaP_5W_{30}O_{110}$ were less effective and led to lower conversions (47%−54%) after 3−4 h. Surprisingly, the vanadium-substituted Keggin-type $H_5PW_{10}V_2O_{40}$ showed a higher activity than the Keggin heteropolyacid, $H_3PW_{12}O_{40}$, which has the highest Brönsted acidity. Moreover, the results confirmed that tungsten-containing heteropolyacids, $H_6P_2W_{18}O_{62}$ and $H_5PW_{10}V_2O_{40}$, were preferred over their molybdenum analogues, $H_6P_2Mo_{18}O_{62}$ and $H_5PMo_{10}V_2O_{40}$, for the synthesis of β-acetamido-β-(4-chlorophenyl)propiophenone. It is difficult to offer an exact explanation for the different catalytic activity patterns observed for these two structural types of heteropolyacids since there is a complex relationship between the activity, structure, and solubility of the polyanion in the reaction medium. By changing the constituent elements of the polyanion (both hetero and addenda atoms), the acid strength of heteropolyacid as well as its catalytic activity and solubility were varied in a wide range [31]. In the case of vanadium-substituted heteropolyacids, the vanadium atom can

Table 1 Synthesis of β-acetamido-β-(4-chlorophenyl)propiophenone in the presence of various heteropolyacids in refluxing acetonitrile



Entry	Heteropolyacid	Amount (mol%)	Time (h)	Temperature (°C)	Yield* (%)	Selectivity (%)
1	$H_5PW_{10}V_2O_{40}$	2.5	0.5	80	88	100
2	$H_7SiW_9V_3O_{40}$	2.5	3	80	86	100
3	$H_3PW_{12}O_{40}$	2.5	3	80	82	100
4	$H_6P_2W_{18}O_{62}$	2.5	3	80	82	100
5	$H_5PMo_{10}V_2O_{40}$	2.5	3	80	77	>98
6	$H_6P_2Mo_{18}O_{62}$	2.5	3	80	53	>95
7	$H_{14}NaP_5W_{30}O_{110}$	0.7	3.5	80	49	>90
8	$H_5SiW_9Mo_2VO_{40}$	2.5	4	80	54	>90
9	$2Na_2O\cdot P_2O_5\cdot 12WO_3$	2.5	4	80	47	>90
10	—	—	10	80	<15	<50
11	$H_5PW_{10}V_2O_{40}$	0.5	1	80	65	>95
12	$H_7SiW_9V_3O_{40}$	0.5	3	80	63	>95
13	$H_5PW_{10}V_2O_{40}$	5	0.4	80	90	100
14	$H_7SiW_9V_3O_{40}$	5	2	80	88	100
15	$H_5PW_{10}V_2O_{40}$	10	0.2	80	93	100
16	$H_7SiW_9V_3O_{40}$	10	0.5	80	92	100
17	$H_5PW_{10}V_2O_{40}$	2.5	0.8	50	60	>95
18	$H_5PW_{10}V_2O_{40}$	2.5	1	25	42	>70
19	ZnO	50	6	80	89	>90
20	ZnO(nano)	10	3	80	91	>90
21	CuO(nano)	10	3	80	88	>90
22	$ZrCl_4$	20	5	80	85	>95
23	$ZrOCl_2$	20	7	80	55	>90
24	ZrO_2	20	3	80	26	>80
25	KH_2PO_4	20	5	80	28	>50
26	L-prolin	20	4	80	<15	>50
27	SiO_2	20	6	80	<15	>50

Reaction conditions: aromatic aldehyde 1 mmol, acetophenone 1 mmol, acetyl chloride 2 mmol, acetonitrile 4 ml. *Isolated yields.

occupy both anionic and cationic positions in the heteropolyanion structure and, subsequently, affects the catalytic activity.

2.2 Effect of $H_5PW_{10}V_2O_{40}$ and $H_7SiW_9V_3O_{40}$ concentrations

First, the four-component coupling condensation of benzaldehyde, acetophenone, and acetyl chloride was performed in acetonitrile in the absence of a catalyst. The reaction was inefficient, and no reaction occurred even after a prolonged reaction time (10 h), indicating that the reaction was indeed a heteropolyacid catalyzed reaction (Table 1, entry 10).

The catalytic activity can be influenced by the parameters such as the kind and amount of the employed catalyst, solvent system, and temperature. To establish the optimal reaction condition, a set of experiments were conducted by changing the catalyst amount, quantity of acetyl chloride, and temperature. Initially, different amount of $H_5PW_{10}V_2O_{40}$ and $H_7SiW_9V_3O_{40}$ were used (Table 1, entries 1, 2, 11−16). The best condition to prepare the β-acetamido ketones was achieved when 2.5 mol% of $H_5PW_{10}V_2O_{40}$ was used. 4-Chlorobenzaldehyde led to 88% product after 0.5 h (entry 1), while a higher amount of catalyst (10 mol%) resulted in 93% conversion in the short time of 0.2 h (entry 15). Employing smaller amounts of the catalyst (0.5 mol%) diminished the product yield to 65% after 1 h. The same reactivity pattern was observed for $H_7SiW_9V_3O_{40}$, but this catalyst was ~3−6 times (depending on catalyst amount) less efficient than $H_5PW_{10}V_2O_{40}$ and led to a maximum conversion of ~90% only after clearly longer times.

2.3 Effect of temperature

The effect of temperature was monitored by carrying out the model reaction in the presence of 2.5 mol% $H_5PW_{10}V_2O_{40}$ in acetonitrile at different temperatures (Table 1, entries 1, 17, and 18). The yield% was increased when the reaction temperature was elevated from 25 to 80 °C. Therefore, the reflux temperature of acetonitrile, 80 °C, was selected for all the reactions.

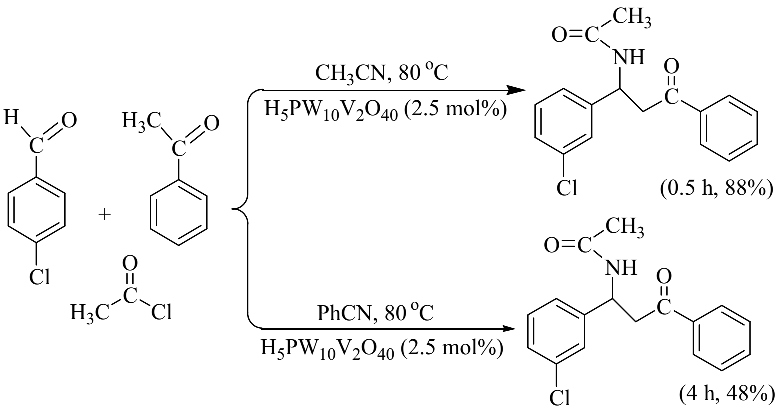
2.4 Effect of the nitrilating agent

It has been demonstrated that the nitrilating agent is a critical parameter in the four-component condensation reaction. Hence, the effect of changing the nitrilating agent from CH_3CN to PhCN was investigated (Scheme 2). Acetonitrile was more efficient than PhCN and led to 88% β-acetamido-β-(4-chlorophenyl)propiophenone after 0.5 h, while phenyl cyanide afforded only 48% yield after 4 h. The optimum amount of acetyl chloride was also studied. 2 equiv. of acetyl chloride was the best. Increasing the volume of acetyl chloride to 4 equiv. resulted in diminishing conversion from 88% to 62% after 0.5 h. Lower amounts of acetyl chloride also led to a decrease in conversion.

2.5 Comparison of the catalytic activity of $H_5PW_{10}V_2O_{40}$ and $H_7SiW_9V_3O_{40}$ with other catalysts

A comparison of the catalytic efficiency of the two examined vanadium substituted heteropolyacids with some selected catalysts is given in Table 1, entries 19–27. Clearly, the heteropolyacids (2.5 mol%) gave excellent activity and led to the highest conversion among the catalysts in relatively short times (entries 1 and 2). The Zr family ($ZrCl_4$, $ZrOCl_2$, and ZrO_2) gave moderate activity and 26%–85% conversion with 20 mol% of catalyst in 3–7 h (entries 22–24). Another distinct feature appears when the catalytic activity of zinc and copper oxides in the bulk and nano-sized forms are compared (entries 19–21). 50 mol% of bulk ZnO led to 89% of conversion after 6 h, while almost the same conversion was achieved with only 10 mol% nano-sized zinc oxide after 3 h. Furthermore, 10 mol% CuO(nano) gave good catalytic activity and β-acetamido-β-(4-chlorophenyl)propiophenone in 88% yield after 3 h. Other catalysts such as SiO_2, L-prolin, and KH_2PO_4 were inefficient, even at high concentrations. These catalysts resulted in < 30% of conversion after prolonged times (entries 25–27).

2.6 Comparing reactivity of acetophenone with other



Scheme 2. Effect of nitrilating agent on the preparation of β-acetamido-β-(4-chlorophenyl)propiophenone.

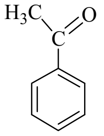
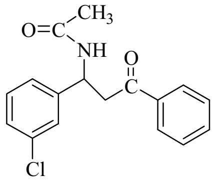
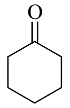
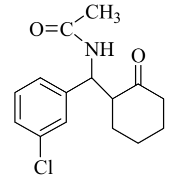
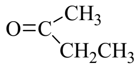
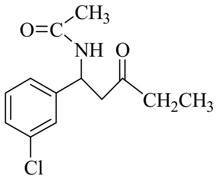
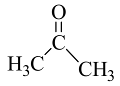
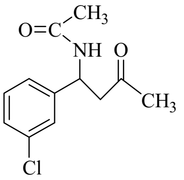
ketones

In addition, the reactivity of acetophenone was compared with other ketones such as cyclohexanone, ethyl methyl ketone, and acetone. The last three ketones gave unsatisfactory results in the reaction with benzaldehyde using the reaction conditions here (Table 2).

2.7 Synthesis of different β-acetamido-β-(aryl)propiophenones catalyzed by $H_5PW_{10}V_2O_{40}$

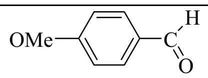
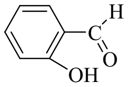
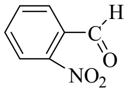
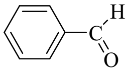
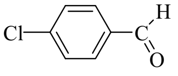
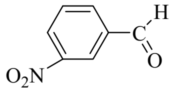
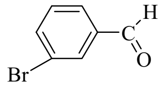
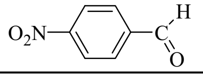
After optimizing the reaction conditions, the present methodology was extended to various substituted aromatic aldehydes (Table 3). The reactions were catalyzed well and the reaction rates as well as the yields were satisfactory. The conversion generally gave the desired product in high yields (69%–97%) within 30–160 min. Aromatic aldehydes containing either electron-donating or electron-withdrawing groups underwent the conversion smoothly. Several functional groups such as halogen (Cl, Br) and NO_2 moieties were found to be stable under the reaction conditions. In the case of the aromatic aldehyde, the electron-withdrawing group on the phenyl ring promoted the reaction. The electron-releasing methoxy group retarded the reaction rate and led to 74% yield for the corresponding product after 100 min. It is noteworthy that no acetylation of an aromatic hydroxyl group was detected when salicylaldehyde (Table 3, entry 2) was used, and the corresponding β-acetamido ketone was isolated in a good yield (69%).

Table 2 Synthesis of β-acetamido-β-(4-chlorophenyl) ketones in the presence of $H_5PW_{10}V_2O_{40}$ in refluxing acetonitrile

Carbonyl compound	Product	Time (h)	Yield (%)	Selectivity (%)
		0.5	88	100
		3	20	50
		4	<15	n.d.
		5	<15	n.d.

Reaction conditions: catalyst 2.5 mol%, aromatic aldehyde 1 mmol, carbonyl compound 1 mmol, acetyl chloride 2 mmol, acetonitrile 4 ml, 80 °C.

Table 3 Synthesis of different β-acoetamido-β-(aryl)propiophenones in the presence of $H_5PW_{10}V_2O_{40}$ in refluxing acetonitrile

Entry	Aldehyde	Time (min)	Yield (%)	Selectivity (%)	Melting point (°C)	
					Found	Reported
1		100	74	100	114–116	115–117 [41]
2		160	69	>95	129–131	130–132 [20]
3		30	77	100	186–188	188–190 [42]
4		40	80	100	103–105	101–103 [20]
5		30	88	100	144–146	144–146 [20]
6		45	79	100	109–111	110–112 [20]
7		40	81	100	101–103	100–103 [36]
8		45	97	100	148–150	150–151 [42]

Reaction conditions: catalyst 2.5 mol%, aldehyde 1 mmol, $PhCOCH_3$ 1 mmol, acetyl chloride 2 mmol, acetonitrile 4 ml, 80 °C.

Table 4 Comparison of the catalytic efficiency of $H_5PW_{10}V_2O_{40}$ with some different catalysts

Catalyst	Amount (mol%)	Time (h)	Yield (%)	Ref.
$H_5PW_{10}V_2O_{40}$	2.5	0.5	88	this work
$ZrOCl_2·8H_2O$	15	12	83	[37]
$ZrCl_4$	20	5	87	[37]
$Zn(OTf)_2$	10	30	60	[19]
$Sc(OTf)_3$	10	30	82	[19]
$BF_3.OEt_2$	100	30	78	[19]
$InCl_3$	100	30	19	[19]
$CuCl_2$	100	30	79	[19]
$LiClO_4$	100	30	59	[19]
Montmorillonite K-10	2 g	7	80	[16]

2.8 Comparison of the catalytic efficiency of $H_5PW_{10}V_2O_{40}$ with other reported catalysts

The superiority of the present method over previously reported methodologies can be seen by comparing the results obtained for the vanadium-substituted heteropolyacid, $H_5PW_{10}V_2O_{40}$, with some previously reported catalysts (Table 4). The reaction of benzaldehyde, acetyl chloride, and acetophenone in acetonitrile was chosen as the model reaction to afford the corresponding β-acetamido-β-phenylpropiophenone. The comparison was based on the amount of the catalyst, reaction time, and percentage yield. Clearly, $H_5PW_{10}V_2O_{40}$ was the best among the catalysts compared.

2.9 Stability and reusability of $H_5PW_{10}V_2O_{40}$

The stability and reusability of a catalyst are very important parameters for industrial use. To establish the reusability of $H_5PW_{10}V_2O_{40}$, the catalyst was washed with dichloromethane and recycled. The recovered catalyst was reused seven times without considerable loss of activity. The results of the first run and subsequent recycles were almost constant in yields (Fig. 1). Thus, the reaction can be carried out with recovered or fresh catalyst with equal efficacy.

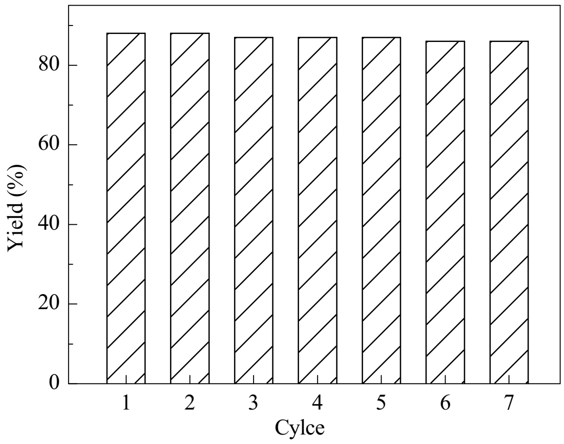


Fig. 1. Reusability of the catalyst.

The stability of the heteropolyacid $H_5PW_{10}V_2O_{40}$ was also investigated by studying the stability of its primary structure after recycling. The primary structure of $H_5PW_{10}V_2O_{40}$ was identified by the characterization of its FT-IR absorption bands [25,32]. As mentioned previously, Keggin-type $H_5PW_{10}V_2O_{40}$ consists of a PO_4 tetrahedron surrounded by four M_3O_{13} groups formed by edge-sharing octahedra (Fig. 2). These groups are connected to each other by corner-sharing oxygens [33], and this arrangement gives rise to four types of oxygen bands between 1200 and 700 cm^{-1}, which is a fingerprint region for Keggin compounds. These characteristic IR bands appear at 1065 cm^{-1} (P–O in central tetrahedral), 947 cm^{-1} (terminal W=O), 846 and 784 cm^{-1}, broad, due to (W–O_b–W) and (W–O_c–W), respectively, associated with the asymmetric vibrations in the Keggin polyanions. Interestingly, the characteristic bands of the Keggin ion for vanadium(V)-containing heteropolyacid were shifted to lower wavenumbers with respect to $H_3PW_{12}O_{40}$. This shift was due to the influence of vanadium (V) on the M–O bond and indicated that changes occurred in the structure symmetry [34]. This shift suggested that vanadium(V) has entered into the primary structure of the Keggin anion of the $H_5PW_{10}V_2O_{40}$ catalyst. Moreover, a shoulder in the P–O stretching vibration was noticed for the $H_5PW_{10}V_2O_{40}$. The splitting of the P–O_d band was reported for a sample with the presence of vanadium(V) in the Keggin structure. It is known that the introduction of a metal other than W into the Keggin ion induces a decrease in the W–O_t stretching frequency and a possible splitting of the P–O_d band. This splitting also suggested the incorporation of V into the Keggin ion [35].

The FT-IR spectra of the recycled catalyst $H_5PW_{10}V_2O_{40}$ after catalytic reaction was checked and the four characteristic peaks mentioned above were observed (Fig. 3). The FT-IR spectra of the fresh and reused catalysts showed no change in the primary Keggin anion even after repeated use. Thus, it was shown that the Keggin structure was intact under the reaction conditions here.

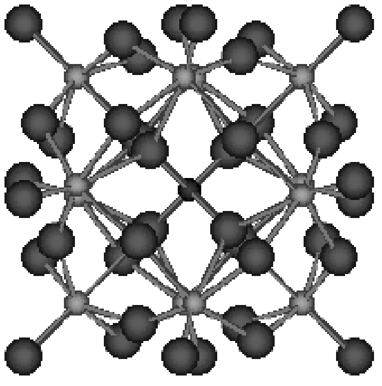


Fig. 2. Structure of Keggin $PM_{12}O_{40}^{3-}$ [30].

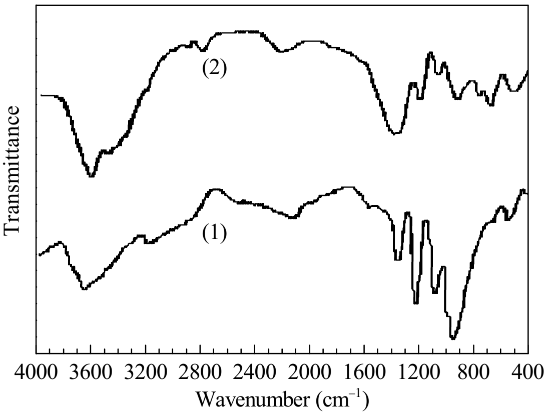
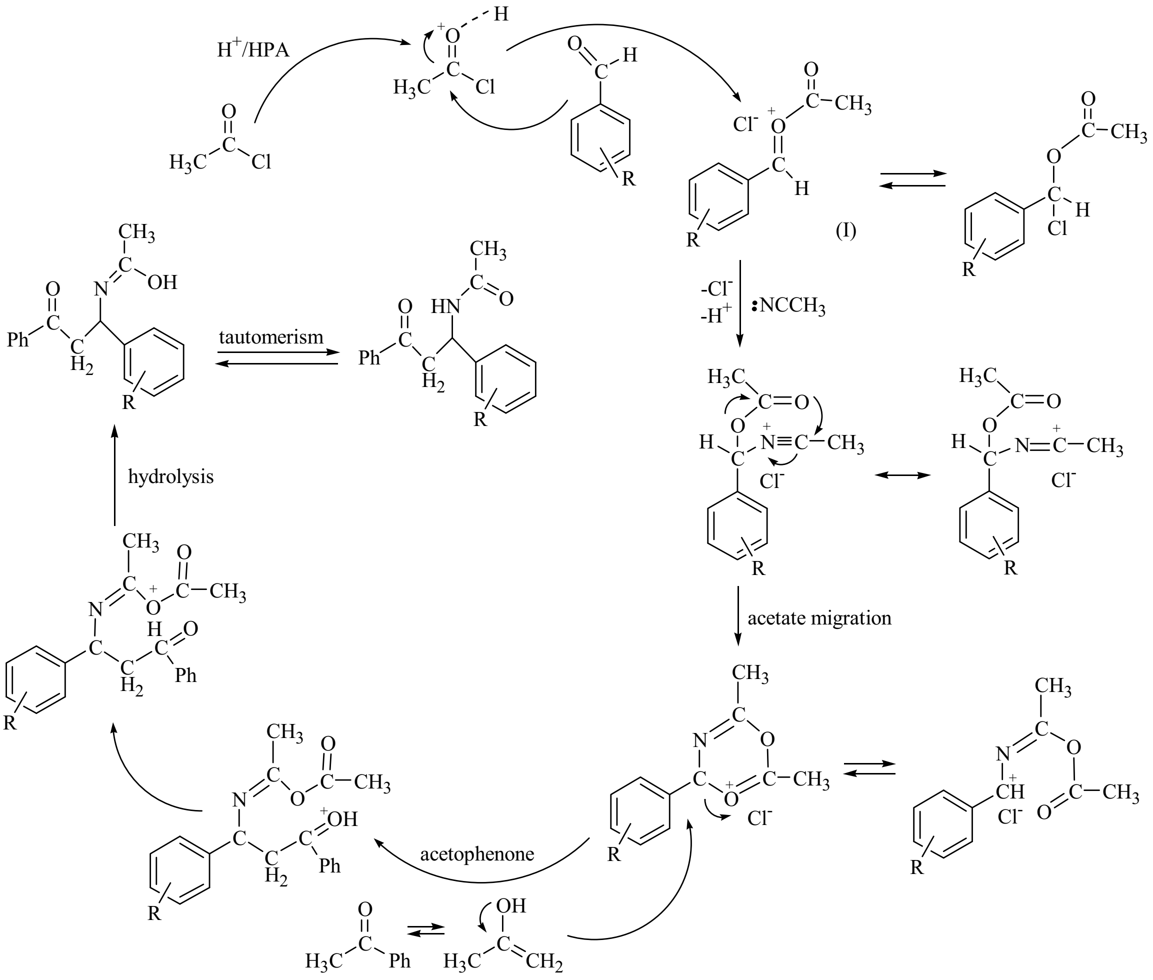


Fig. 3. FT-IR spectra of fresh (1) and recycled catalyst after the 7th run (2).

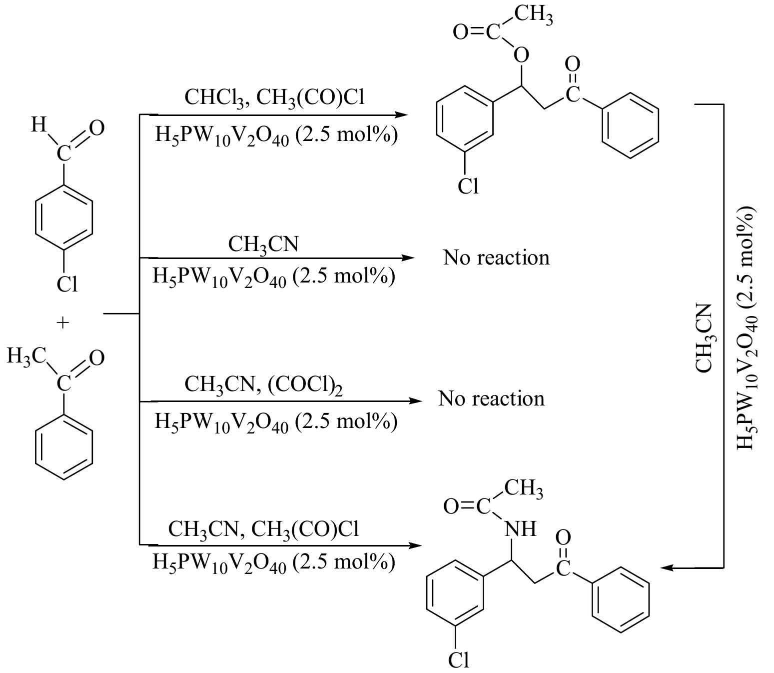
2.10 Reaction pathway

It is not exactly clear how $H_5PW_{10}V_2O_{40}$ catalyzes the reaction, so we used previously reported mechanisms [20,36–40] to suggest the reaction pathway in Scheme 3. The mechanism involves acylation of the aldehyde with acetyl chloride and formation of α-chloroacetate as intermediate (I). Then, this intermediate reacts with acetonitrile to afford the corresponding α-acetoxy amide, which further combines with the enolate form of acetophenone to afford the imidate ester and, finally, the amide product. The protonation of the aldehyde activates the carbony group for nucleophillic attack. Moreover, it can be suggested that the V–O–M and V=O centers would be the active sites of the vanadium-substituted heteropolyacids, which participate in the activation of aldehyde carbonyl group. Therefore, the heteropolyacid not only functioned as a Brönsted acid but also as a Lewis acid in the reaction mechanism.

The role of substituents in the enolizable ketone and aldehydes on the efficiency and yield was studied in detail. In the case of the enolizable ketone, electron-withdrawing groups in the para position enhanced the rate of reaction and yield compared to electron-donating groups. This behavior was attributed to the promoting enolization of the active methylene group to facilitate the reaction, resulting in higher yield and less reaction time. The same argument can be used for the poor reactivity of cyclohexanol, acetone, and ethyl methyl ketone. In the case of the aldehydes, electron-withdrawing groups in the para position promoted the reaction, while elec-



Scheme 3. Reaction pathway for the one-pot condensation of an aryl aldehyde, acetophenone, acetyl chloride, and acetonitrile.



Scheme 4. Some Mechanistic information on the heteropolyacid catalyzed synthesis of β-acetamido-β-(4-chlorophenyl)propiophenone.

tron-releasing substituents were detrimental to the reaction. This was confirmed by the observation that electron-releasing groups such as CH_3, OCH_3, and $N(CH_3)_2$ at the para position of the aldehydes retarded the reaction.

Further FT-IR characterization of the reaction mixture led to some important mechanistic information for the multicomponent reaction according to the schemes 3 and 4 as follows.

(1) No β-acetamido ketone was observed when a mixture of benzaldehyde, acetophenone, acetic anhydride and heteropolyacid catalyst in acetonitrile were reacted even after a prolonged time.

(2) The reaction of 4-chlorobenzaldehyde with acetophenone in acetonitrile failed to provide the desired product in the absence of acetyl chloride. This clearly indicated the key role of acetyl chloride in the reaction.

(3) Using oxalyl chloride as a source of chloride ion, instead of acetyl chloride, in the reaction of 4-chlorobenzaldehyde with acetophenone in acetonitrile was also unsuccessful. This observation clearly demonstrated that the chloride ion did not contribute to the condensation reaction.

(4) The reaction of 4-chlorobenzaldehyde, acetophenone, and acetyl chloride in chloroform, instead of acetonitrile, led to the formation of the corresponding β-acetoxy ketone. This product was consequently converted to the corresponding β-acetamido ketone by further treatment with acetonitrile.

(5) As described in 2.4 (Scheme 2), acetyl chloride was not incorporated into the final product and acetonitrile itself is the N-donor and nucleophile. Using benzonitrile instead of acetonitrile gave the generation of benzamide. This observation clearly confirmed that nitrile acted not only as a solvent but also as a nitrogen donor.

3 Conclusions

This paper described a convenient and efficient process for the synthesis of β-acetamido ketones through the four-component coupling of aromatic aldehydes, enolisable ketone, and acetyl chloride in acetonitrile using vanadium(V)-containing heteropolyacids, especially $H_5PW_{10}V_2O_{40}$, as cheap, commercial, non-corrosive, and environmentally benign catalysts. The present methodology offers attractive features such as simple procedure combined with easy workup, relatively short reaction times, and high yields, and would have wide scopes in organic synthesis. This protocol is recommended as a useful and attractive strategy for the large scale synthesis of β-acetamido ketones.

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