DOI 10.5012/bkcs.2010.31.12.3653

# Silica Supported Tungstosilicic Acid as an Efficient and Reusable Catalyst for the One-Pot Synthesis of β-Acetamido Ketones *via* a Four-Component Condensation Reaction

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*Received August 19, 2010, Accepted October 7, 2010*

Silica supported tungstosilicic acid has been used as an effective catalyst for a modified Dakin-West one-pot, four-component condensation of an aryl aldehyde, an aryl ketone, acetyl chloride and acetonitrile for the synthesis of β-acetamido ketones. This catalytic system can act as an active, inexpensive, recoverable and recyclable catalyst. Some advantages of this system are short reaction times, good to excellent yields, easy work up and the ability to be carried out at the large scale reactions.

**Key Words**: β-Acetamido ketone, Silica supported tungstosilicic acid, Four-component, Dakin-West reaction

## Introduction

Heteropoly acids (HPAs) are a unique class of active materials in both redox and acid catalysis,[1-3] which are widely used as catalysts in various reactions. HPAs with Keggin structure are the most studied class within polyoxometalates, because they possess relatively high thermal stability[4] and acidity,[5] and, 12-tungstophosphoric acid and 12-tungstosilicic acid are the usual catalysts of choice because of their high acidic strength, relatively high thermal stability, and lower oxidation potential. HPAs can be used either directly as a bulk material or in supported form in both homogeneous and heterogeneous systems. They are highly soluble in polar solvents but insoluble in non-polar ones. Some advantages of HPAs are non-corrosive, environmentally friendly because of its reusability, economically feasible solid acid catalysts compared to conventional homogeneous acids, high flexibility, in modification of the acid strength, ease of handling, non-toxicity and experimental simplicity.[6] From the synthetic point of view, a variety of useful transformations such as oxidation of alcohols,[7] Friedel-Crafts[8] and Mannich reactions,[9] cyanosilylation,[10] ring-opening of epoxides,[11] and dehydration,[12] have been developed using HPAs as catalysts. Increasing of the surface area or even better, increasing of the number of accessible acid sites of the HPAs is important. This can be achieved by dispersing the HPAs on solid supports with high surface area.[13-15] These supported catalysts have been widely studied and found useful in many reactions such as the synthesis of 2,4-dihydropyrimidones,[16] metanethole,[17] α-aminonitriles[18] and esterification.[19,20]

The β-acetamido carbonyl compounds, in that their skeletons exist in a number of valuable biologically or pharmacologically active compounds,[21,22] has gained considerable attention in organic synthesis, owing to their importance as versatile intermediates for preparation of β-amino acids,[23] or 1,3-amino alcohols[24] as well as for the synthesis of various antibiotics such as nikkomycins or neopolyoxines[25] and potent molecules in α-glucosidase inhibitory activity.[26]

β-Acetamido ketones were usually prepared through Michael addition to α,β-unsaturated ketones,[27] acylation of β-aminoketones,[28] or photoisomerisation of phthalimides.[29]

The Dakin-West reaction is the conventional way for the synthesis of β-acetamido ketones, involving condensation of an α-aminoacid with acetic anhydride in the presence of a base *via* an intermediate azalactone.[30] Iqbal and coworkers reported the best known route for the synthesis of β-acetamido carbonyl compounds in the one-pot condensation of an aldehyde, an enolizable ketone, acetyl chloride, and acetonitrile catalyzed both $CoCl_2$[31] and Montmorillonite K-10 clay.[32] A few catalysts have already been applied for the synthesis of β-acetamido ketones using this method, including Sn(II),[33] Sc(III) triflates,[34] $InCl_3$,[34] $H_2SO_4/SiO_2$,[35] Zirconia,[36] ZnO,[37] phosphotungstic acid,[38] sulfamic acid,[39a] aluminium hydrogen sulfate,[39b] $CeCl_3$,[40] cerium(IV) sulfate,[41] and Nafion-H.[42] The role of these acidic catalysts is activation of the carbonyl group of the aldehyde toward the addition of acetonitrile[43,44] or toward the attack of the enole of aryl ketone.[45] These methods are valuable but they suffer from different drawbacks such as hazardous reagents, high temperature, expensive catalysts, long reaction time, tedious work-up and low yield. Hence, the development of a simple and new protocol with more efficiency is still in demand.

Multicomponent reactions (MCRs) have proved to be remarkably successful in generating highly complex structures in a single synthetic step operation.[46] This process has emerged as an efficient and powerful tool in modern synthetic chemistry allowing the facile creation of several new bonds in a one-pot transformation. The organic chemists have transformed this powerful technology into one of the most efficient and economic tools for parallel and combinatorial synthesis.[47] One eminent MCR that produces an interesting class of compounds is the Dakin-West reaction, which is a powerful synthetic method for the preparation of β-acetamido carbonyl compounds.

It is, therefore, interesting to find out the behavior of a new catalytic system in the synthesis of β-acetamido ketones in a one-pot multicomponent way.

## Experimental

Chemicals were purchased from Merck, Fluka and Aldrich

chemical companies. All of the products were identified by comparison of their physical and spectral data with those of authentic samples. IR spectra were recorded on a JASCO-FTIR-680 spectrophotometer. $^1$H NMR spectra were obtained with a Bruker 400 Ultrasheild (400 MHz) spectrometer.

**Preparation of the supported catalyst.** The silica gel supported $H_4SiW_{12}O_{40}$ was prepared by mixing silica gel (1.4 g, Merck grade 40, 0.063 - 0.2 mm) with a solution of acid (0.60 g) in distilled water (20 mL). The resulting mixture was stirred for 30 min. After removal of water in a rotary evaporator, the solid powder was dried at 80 °C for 4 h followed by 4 h calcinations at 170 °C.

**General procedure for the preparation of β-acetamido ketones.** A mixture of the aryl aldehyde (1 mmol), aryl ketone (1 mmol), acetyl chloride (0.3 mL) and acetonitrile (2 mL) in the presence of $H_4SiW_{12}O_{40}$-$SiO_2$ (0.1g, equal to 0.04 mmol $H^+$) was heated at 80 °C, with stirring for 20 - 60 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the filtrate was poured into 50 mL ice-water. The solid product was filtered, washed with ice-water and recrystallized from ethyl acetate/*n*-heptane to give the pure products in 75 - 92% yields based on the starting aldehyde (Table 3). Spectroscopic data of new compounds:

***N*-[3-(4-Nitrophenyl)-1-(2,6-dichlorophenyl)-3-oxopropyl] acetamide (Table 3, entry 25):** mp 78 - 81 °C; $R_f$= 0.43 (*n*-hexane:ethyl acetate = 1:4); IR [(KBr) cm$^{-1}$]: 3406, 3105, 1689, 1674, 1605, 1520, 1428, 1400, 1324,1150, 1008, 856, 740, 670, 618; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.70 (dd, *J* = 8.0 and *J* = 16.8 Hz, 1H), 3.76 (dd, *J* = 8.2 and *J* = 16.4 Hz, 1H), 6.56 (m, 1H), 7.18-7.36 (m, 3H), 8.15 (d, *J* = 8.0 Hz, 2H), 8.33 (d, *J* = 7.6 Hz, 2H); $^{13}$C NMR ($CDCl_3$), δ 23.42, 42.95, 48.08, 128.73, 129.67, 129.45, 129.87, 130.26, 132.65, 134.07, 135.42, 139.43, 170.45, 198.23. Anal. Calcd. for $C_{17}H_{14}Cl_2N_2O_4$: C, 53.56; H, 3.70;; N, 7.35; Found: C, 53.4; H, 3.7; N, 7.2.

***N*-[3-(4-Methoxyphenyl)-1-(2-nitrophenyl)-3-oxopropyl] acetamide (Table 3, entry 26):** mp 170 - 172 °C; $R_f$ = 0.45 (*n*-hexane:ethyl acetate = 1:4); IR [(KBr) cm$^{-1}$]: 3290, 3080, 1675, 1648, 1587, 1520, 1448, 1250, 985, 820, 675, 598; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.01(s, 3H), 3.59 (dd, *J* = 7.8 and 15.2 Hz, 1H), 3.61 (dd, *J* = 7.2 and 15.4 Hz, 1H), 5.93 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 6.2 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.94 (t, *J* = 7.2 Hz, 2H); $^{13}$C NMR ($CDCl_3$), δ 23.25, 41.70, 47.57, 55.54, 113.98, 124.97, 128.23, 129.60, 129.87, 130.72, 132.22, 133.45, 135.50, 138.31, 169.89, 198.58. Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18; Found: C, 63.0; H, 5.2; N, 8.1.

***N*-[3-(4-Methoxyphenyl)-1-(2,4-dichlorophenyl)-3-oxopropyl]acetamide (Table 3, entry 27):** mp 188 - 190 °C; $R_f$= 0.55 (*n*-hexane:ethyl acetate = 1:4) ; IR [(KBr) cm$^{-1}$]: 3298, 3089, 1672, 1645, 1592, 1550, 1405, 1280, 1256, 1150, 990, 820, 668, 592; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 3H), 3.37 (dd, *J* = 5.6 and 16.4 Hz, 1H), 3.69 (dd, *J* = 5.6 and 16.8 Hz, 1H), 3.88 (s, 3H), 5.74 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.2, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.40 (m, *J* = 8.2 Hz, 2H), 7.88 (d, *J* = 7.6 Hz, 2H); $^{13}$C NMR ($CDCl_3$), δ 23.16, 26.97, 42.39, 46.94, 114.38, 123.87, 123.96, 126.56, 126.58, 129.31, 129.33, 129.60, 138.42, 146.23, 175.62, 198.87. Anal. Calcd. for $C_{18}H_{17}Cl_2NO_3$: C, 59.03; H, 4.68; N, 3.82; Found: C, 58.9; H, 4.6; N, 3.9.

***N*-[3-(3-Nitrophenyl)-1-(4-nitrophenyl)-3-oxopropyl]acetamide (Table 3, entry 28):** mp 157 - 159 °C; $R_f$= 0.49 (*n*-hexane: ethyl acetate = 1:4); IR [(KBr) cm$^{-1}$]: 3300, 3090, 1692, 1642, 1607, 1424, 1325, 1125,1105, 670,593; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 3.41 (dd, *J* = 6.5 and *J* = 17.5 Hz, 1H), 3.72 (dd, *J* = 6.5 and *J* = 18.0 Hz, 1H), 5.55 (m, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.59 (dd, *J* = 9.0 Hz, *J* = 16.5 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.17 (m, 1H), 8.31 (dd, *J* = 8.5 Hz, *J* = 17 Hz, 2H), 8.65 (d, *J* = 9.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$), δ 23.15, 42.34, 49.06, 122.93, 128.72, 132.81, 134.85, 135.92, 137.44, 146.86, 148.72, 149.41, 151.78, 169.45, 198.75. Anal. Calcd. for $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23; N, 11.76; Found: C, 57.0; H, 4.1; N, 11.8.

## Results and Discussion

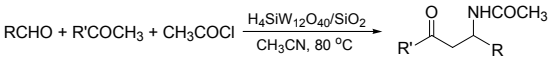
In continuation of our ongoing research program on tungstosilicic acid,[48] we wish to report a convenient and efficient procedure for the synthesis of β-acetamido ketones in the presence of catalytic amounts of tungstosilicic acid supported on $SiO_2$ (Scheme 1).

**Preparation of the silica supported 12-tungstosilicic acid.** The supported tungstosilicic acid catalyst were prepared by the method of incipient wetness. In a typical procedure, a 600 mg portion of acid was dissolved in deionized water (50 mL) and impregnated drop-wise onto 1400 mg supports under constant agitation. The resulting pastes were dried at 80 °C for 4 h and then calcined at 170 °C for 4 h.[49]

FT-IR spectra can be used as a powerful technique for the investigation of surface interaction between tungstosilicic acid and inorganic support. Pure acid compound display infrared bands at 980 (W=O), 925 (Si-O), 880 (W-$O_d$-W) and 781 cm$^{-1}$ (W-$O_b$-W).[50] In addition, a broad, intense band centered around 3450 cm$^{-1}$ (νO-H stretching) and a weak absorption at 1640 cm$^{-1}$ ($\delta H_2O$ bending) indicate the presence of water.

However, small shifts of $\nu W{=}O_d$ (973 cm$^{-1}$) and $\nu W$-$O_c$-W (790 cm$^{-1}$) vibrations were registered indicating interactions of the support with the most external atoms $O_d$ and $O_c$ of the Keggin anion. Such effects are decreased with the increasing coverage.

**Effect of tungstosilicic acid loading on $SiO_2$.** For investigation of the effect of different amounts of $H_4SiW_{12}O_{40}$ loading on




**Scheme 1**

**Table 1.** Effect of $H_4SiW_{12}O_{40}$-$SiO_2$ weight ratios in the synthesis of *N*-(1,3-diphenyl-3-oxopropyl) acetamide from benzaldehyde and acetophenone

| Entry | $H_4SiW_{12}O_{40}$-$SiO_2$ (wt %) | Time (min) | Yields (%)[a] |
|---|---|---|---|
| 1 | 10 | 80 | 60 |
| 2 | 20 | 35 | 82 |
| 3 | 30 | 20 | 90 |
| 4 | 40 | 15 | 92 |

[a]Isolated yields

**Table 2.** Investigation of catalyst amount effect in the synthesis of *N*-(1,3-diphenyl-3-oxopropyl) acetamide from benzaldehyde and acetophenone[a]

| Entry | Amount of catalyst (g) | Supported tungstosilicic acid (mol %) | Time (min) | Yields (%)[b] |
|---|---|---|---|---|
| 1 | 0.025 | 0.26 | 85 | 50 |
| 2 | 0.05 | 0.52 | 60 | 78 |
| 3 | 0.075 | 0.78 | 35 | 85 |
| 4 | 0.1 | 1.04 | 20 | 90 |
| 5 | 0.125 | 1.3 | 20 | 92 |

[a]30% $H_4SiW_{12}O_{40}$-$SiO_2$ was used as catalyst. [b]Isolated yields.

support in the synthesis of β-acetamido ketones, various weight percents of acid were used. Table 1 shows differences in catalytic activity among catalysts having 10 - 40 wt % of $H_4SiW_{12}O_{40}$ on silica. Lowering the loading of the deposited tungstosilicic acid causes the reduction of the catalytic activity. No improvement in the reaction rates and yields was observed by increasing the amount of acid on $SiO_2$ from 30 to 40 wt %. Since 30 wt % of $H_4SiW_{12}O_{40}$-$SiO_2$ was the best catalyst loading, it was used to study the effect of various parameters on yields.

**Effect of catalyst concentration.** The catalyst concentration was varied over a range of 0.025 - 0.125 g (0.26 - 1.3 mol % of supported tungstosilicic acid) on the basis of the total volume of the reaction mixture. Table 2 shows the effect of catalyst concentration on the reaction of benzaldehyde and acetophenone. The yield of the corresponding β-acetamido ketones increased with increasing of catalyst concentration from 0.26 to 1.04 mol %. Further addition of catalyst had no noticeable effect on the yield. This was due to the fact that beyond a certain concentration, there exist an excess of catalyst sites over what is actually required by the reactant molecules, and hence, the additional catalyst does not increase the rate of the reaction. Therefore, in all further reactions 1.04 mol % was used for 30 wt % of $H_4SiW_{12}O_{40}$-$SiO_2$.

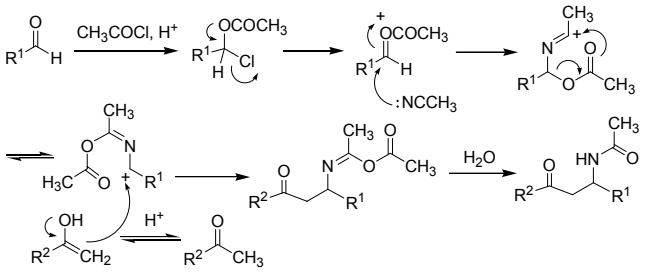
**Synthesis of β-acetamido ketones catalyzed by supported tungstosilicic acid.** The results from the reactions of aryl aldehydes, aryl methyl ketones and acetyl chloride in the presence of optimized $H_4SiW_{12}O_{40}$-$SiO_2$ in acetonitrile at 80 °C are shown in Table 3. The experimental procedure for this reaction requires no inert atmosphere. Both aromatic aldehydes and acetophenones bearing either activating or deactivating groups underwent transformation well to the corresponding β-acetamido ketones, without the formation of any side products, in high to excellent yields (Entries 1-29). All reactions were completed within 20 - 60 min. It is noteworthy that no acetylation of aromatic hydroxyl groups were observed under the reaction conditions and the corresponding β-acetamido ketones were isolated in good yields (Table 3, entries 24 and 29). We observed that aliphatic aldehydes react under these conditions, but produce the corresponding product in low yields (Table 3, entry 30).

To use of $H_4SiW_{12}O_{40}$-$SiO_2$ in large scale synthesis especially in chemical laboratory, a typical reaction was performed for synthesis of **1** with tenfold amounts of reactants and catalyst with respect to one mentioned in the experimental section. The result showed the yield of 85% in this condition which is comparable with one in Table 3.

**Table 3.** Synthesis of β-acetamido ketones in the presence of $H_4SiW_{12}O_{40}$-$SiO_2$

| Entry | R | R' | Time (min) | Yield[a,b] (%) |
|---|---|---|---|---|
| **1** | $C_6H_5$- | $C_6H_5$- | 20 | 90 |
| **2** | 3-$NO_2C_6H_4$- | $C_6H_5$- | 60 | 80 |
| **3** | 4-$NO_2C_6H_4$- | $C_6H_5$- | 50 | 82 |
| **4** | 2-$NO_2C_6H_4$- | $C_6H_5$- | 45 | 90 |
| **5** | 4-$ClC_6H_4$- | $C_6H_5$- | 30 | 90 |
| **6** | 2-$ClC_6H_4$- | $C_6H_5$- | 25 | 90 |
| **7** | 4-$BrC_6H_4$- | $C_6H_5$- | 25 | 90 |
| **8** | $C_6H_5$- | 4-$BrC_6H_4$- | 35 | 87 |
| **9** | 3-$NO_2C_6H_4$- | 4-$BrC_6H_4$- | 40 | 87 |
| **10** | 4-$NO_2C_6H_4$- | 4-$BrC_6H_4$- | 45 | 86 |
| **11** | 4-$ClC_6H_4$- | 4-$BrC_6H_4$- | 30 | 89 |
| **12** | 2-$ClC_6H_4$- | 4-$BrC_6H_4$- | 20 | 92 |
| **13** | 4-$BrC_6H_4$- | 4-$BrC_6H_4$- | 30 | 90 |
| **14** | 2,4-$Cl_2C_6H_3$- | 4-$BrC_6H_4$- | 35 | 85 |
| **15** | 2-Cl-6-F-$C_6H_3$- | 4-$BrC_6H_4$- | 50 | 83 |
| **16** | $C_6H_5$- | 4-$NO_2C_6H_4$- | 35 | 80 |
| **17** | 3-$NO_2C_6H_4$- | 4-$NO_2C_6H_4$- | 50 | 80 |
| **18** | 4-$NO_2C_6H_4$- | 4-$NO_2C_6H_4$- | 50 | 76 |
| **19** | 4-$ClC_6H_4$- | 4-$NO_2C_6H_4$- | 30 | 85 |
| **20** | 4-$BrC_6H_4$- | 4-$NO_2C_6H_4$- | 40 | 92 |
| **21** | 4-$FC_6H_4$- | 4-$NO_2C_6H_4$- | 40 | 75 |
| **22** | 4-$OCH_3C_6H_4$- | 4-$NO_2C_6H_4$- | 25 | 78 |
| **23** | 4-$CH_3C_6H_4$- | 4-$NO_2C_6H_4$- | 40 | 75 |
| **24** | 2-$OHC_6H_4$- | 4-$NO_2C_6H_4$- | 35 | 85 |
| **25** | 2,6-$Cl_2C_6H_3$- | 4-$NO_2C_6H_4$- | 50 | 87 |
| **26** | 2-$NO_2C_6H_4$- | 4-$CH_3O$- | 40 | 84 |
| **27** | 2,4-$Cl_2C_6H_3$- | 4-$CH_3O$- | 35 | 90 |
| **28** | 4-$NO_2C_6H_4$- | 3-$NO_2C_6H_4$- | 50 | 75 |
| **29** | 2-$OHC_6H_4$- | 3-$NO_2C_6H_4$- | 30 | 80 |
| **30** | $CH_3CH_2CH_2$- | $C_6H_5$- | 120 | 25 |

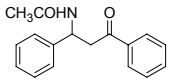
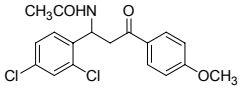
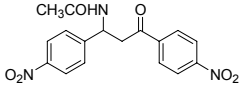
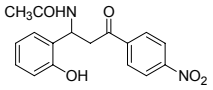
[a]All products were characterized by $^1H$ NMR, $^{13}C$ NMR and IR spectroscopy and compared with those reported in the literature.[31,41,42] [b]Isolated yields.




**Scheme 2**

The plausible mechanism for the formation of β-acetamido ketones is shown in Scheme 2. The presence of acetyl chloride is necessary for the transformation and the desired product in its absence was not prepared even after 3 h. The mechanism may involve α-chloroacetate from aldehyde and acetyl chloride. On further reaction with acetonitrile it affords the corresponding α-acetoxyamides which will react with the enolate form of the

**Table 4.** Synthesis of some β-acetamido ketones in the presence of $H_4SiW_{12}O_{40}$

| Entry | Product | $H_4SiW_{12}O_{40}$ | | $H_4SiW_{12}O_{40}$-$SiO_2$ | |
|---|---|---|---|---|---|
| | | Time (min) | Yields[a] (%) | Time (min) | Yields (%) |
| 1 |  | 100 | 55 | 20 | 90 |
| 2 |  | 140 | 60 | 35 | 90 |
| 3 |  | 200 | 40 | 50 | 76 |
| 4 |  | 120 | 37 | 35 | 85 |

[a]Isolated yields.

ketone to afford the imidate ester and then will yield the amide.

To achieve the reaction efficiency of recovered catalyst, the reaction mixture of **1** was filtered and washed with hot acetonitrile twice to give recovered silica supported tungstosilicic acid. The recovered catalyst was used again for the synthesis of **1** that led to the yield of 84%. The recovered catalyst can be reused at least four times without noticeable losing activity.

**Effect of unsupported acid in synthesis of β-acetamido ketones.** As shown in Table 4, in the presence of tungstosilicic acid without supporting on $SiO_2$, the synthesis of β-acetamido ketones were performed in longer time with reduced yields in comparison with supported one. For example, in presence of $H_4SiW_{12}O_{40}$-$SiO_2$, the reaction of benzaldehyde and acetophenone (entry 1) was completed in 20 min, while by using of unsupported catalyst this reaction was carried out in 100 min with 50% yield. This results show that supporting of tungstosilicic acid on $SiO_2$ accelerates catalytic strength of this catalyst.

**Effect of $SiO_2$ in synthesis of β-acetamido ketones.** For investigation of the probable effect of $SiO_2$ as catalyst in the synthesis of β-acetamido ketones, various weight percents of silicagel were used. In the synthesis of *N*-(1,3-diphenyl-3-oxopropyl) acetamide from benzaldehyde and acetophenone in the presence of $SiO_2$, the reaction was carried out in 12 h in 20% yield while in the presence of $H_4SiW_{12}O_{40}$-$SiO_2$, the reaction of benzaldehyde and acetophenone was completed in 20 min and by using of unsupported catalyst, this reaction was carried out in 100 min with 55% yield (Table 4). These results show that both supported and unsupported $H_4SiW_{12}O_{40}$ accelerate rate of reaction *versus* $SiO_2$ alone.

## Conclusion

We have reported an efficient, inexpensive and straightforward procedure for one-pot synthesis of β-acetamido ketones using $H_4SiW_{12}O_{40}$-$SiO_2$ as catalyst. The catalyst can be easily prepared and can be handled safely. Moreover, non-hygroscopic and inexpensive characteristics for this transformation are other advantages of this procedure. The simple experimental procedure combined with the easy workup and good to excellent yields of products are salient features of the presented method.

**Acknowledgments.** We are thankful to Yasouj University for partial support of this work.

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