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Application of silica vanadic acid as a dual Lewis and Bronsted acid catalytic ability in Dakin West reaction

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ABSTRACT

Silica Vanadic Acid, SVA, (oxo-vanadium has been supported on silica) as a dual Lewis and Bronsted acid ability was prepared and efficiently catalyzed one-pot multi-component condensation of enolizable ketones or alkyl acetoacetates with aromatic aldehydes, acetonitrile and acetyl chloride. The described reaction was produced *β*-acetamido ketone or ester derivatives in high to excellent yields in relatively short reaction times in heterogeneous catalytic system at room temperature. Other advantages of this method is applicable at large scales without significant loss of the yields. In addition, this method is superior to reported methods, for the synthesis of β-acetamido ketone or ester derivatives.

Keywords: *β-Acetamido ketone, β-Acetamido ester, Silica vanadic acid (SVA), Enolizable ketone, Multi-component reactions, Dakin west.*

1. Introduction

Development of heterogeneous catalysts for fine chemicals synthesis has become a major area of research. One of the major disadvantages of the homogeneous catalysts is the difficulty in separating the expensive catalysts from the reaction mixture at the end of the process.

Immobilization of the homogeneous catalysts through grafting with silica gel is one of the most specialized methods to heterogenization of homogeneous catalysts. This inorganic supporter has some advantageous properties such as excellent stability, good availability and high surface area which will be beneficial to the enhancement of loading amount and dispersion of catalytic action [1]. Therefor design heterogenized metal catalysts represents a rapidly growing field that has been significantly applied in industry.

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Vanadium is a very special metal with unique mechanical properties. Also it is the most important metal used in metal oxide catalysis. So, catalysts containing vanadium oxides are known to be highly efficient catalysts in many oxidation reactions [2].

Multi-component reactions (MCRs) have received considerable attention in modern organic synthesis and medicinal chemistry because they are powerful synthetic tools for the one-pot synthesis of biologically active compounds and show high atom economy and high selectivity [3-4].

β-Acetamido ketone or ester derivatives are useful building blocks for a number of biologically and pharmaceutically valuable compounds. These are precursors of molecules such as 1,3-amino alcohols, and structural scaffolds found in natural nucleoside peptide antibiotics such as nikkomycins or neopolyoxins [5-8]. The structural and bioactive properties of β-acetamido carbonyl compounds led to the generation of some processes employing some catalysts such as montmorillonite K10 [9], $CoCl_2$ [10-12], $H_6P_2W_{18}O_{62}$ [13], $H_3PW_{12}O_{40}$, [14], $Zr(HSO_4)_4$ and $Mg(HSO_4)_2$ [15], TMSCl [16], $BiCl_3$ generated from

BiOCl [17], I_2 [18] , silica sulfuric acid [19], ZnO [20] , selectfluorTM [21], sulfamic acid [22], and $ZrOCl_2.8H_2O$ [23].

All of these methods while offering some advantages also suffer from different drawbacks such as the use of expensive catalysts, longer reaction times, high temperature, low yields, tedious work-up procedure and the use of large amount of catalyst.

The aim of the present study is to provide and application of heterogeneous vanadium oxide as a strong Lewis and Bronsted acid ability (Scheme 1) for the synthesis of β-acetamido ketones and esters via the one-pot multi-component condensation reaction between enolizable ketones or alkyl acetoacetates, aldehydes, acetonitrile and acetyl chloride at room temperature.

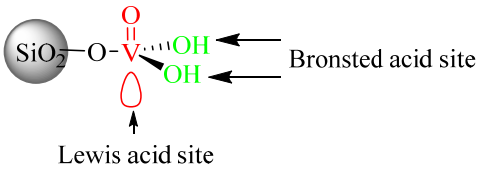
2. Experimental

2.1. Synthesis of silica vanadic acid

In a 100 ml round-bottomed flask, *n*-hexane (25 mL) and silica gel (4.0 g) were stirred for 10 min and then vanadiumoxytrichloride (4.0 *g*) was dissolved in *n*-hexane (25 mL) and added drop wise to silica gel suspension during 15-20 min and after addition of $VOCl_3$, the red-brown mixture was stirred for 10 hours. Then, solvent was evaporated and the residue (the red-brown powder (II) was obtained after the grafting process) was filtered, washed with dry *n*-hexane several times to remove unreacted $VOCl_3$, dried under vacuum, and stirred in the air for 72 hours to promote the hydrolysis of V–Cl bonds (Scheme 2). At this time the red-brown powder changed to dark green powder (III) slowly [24-26]. Typical loading of vanadium was determined using X-ray fluorescence (XRF) and showed a loading 8±0.1 mmol g^{-1}.

2.2. General procedure for the synthesis of β-acetamido carbonyl compounds:

To a stirred solution of enolizable ketone or alkyl acetoacetate (1 mmol) and aldehyde (1 mmol) in acetonitrile (3 mL) were added acetyl chloride (0.3 mL) and silica vanadic acid (0.03 g, 24mol%) and the resulting mixture was stirred at room temperature.



Scheme 1. Silica Vanadic Acid (SVA).

After completion of the reaction, as monitored with TLC, crushed ice (10 mL) was added to the reaction mixture and stirred thoroughly. On solidification, the crude product was filtered off, dried, and purified by short column chromatography on silica gel eluted with EtOAc/*n*-hexane (1/4). All of the product was characterized by their physical and spectral data and provided as a supplementary file.

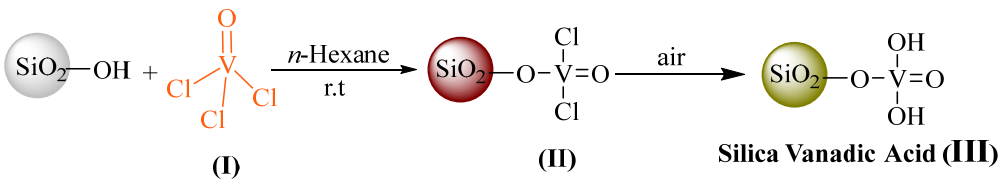
3. Results and Discussion

Herein, we report a mild and efficient protocol for the preparation of β-acetamido carbonyl compounds by four-component reactions of an aromatic aldehyde, acetonitrile, an enolizable ketone or β-keto ester and acetyl chloride, catalyzed by SVA at room temperature (Scheme 3).

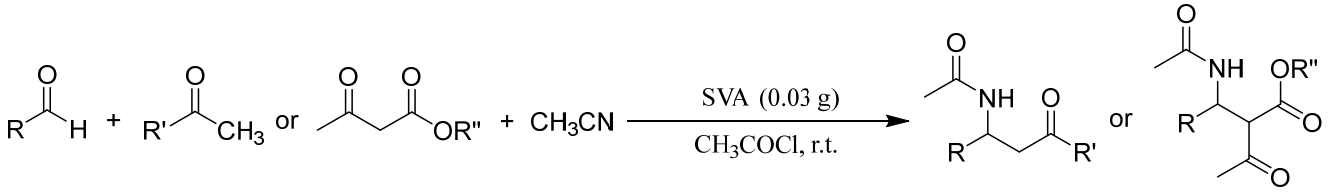
The reaction was tested using different amounts of SVA at room temperature. The best amount of the catalyst was 0.03g or 24 mol% (Table 1).

To assess generality and efficacy of the method, different enolizable carbonyl compounds were reacted with structurally and electronically diverse aldehydes, acetonitrile and acetyl chloride under the optimized reaction conditions and the results are summarized in Table 2. Both aromatic aldehydes and acetophenones with activating and deactivating groups underwent smooth transformation to the corresponding β-acetamido ketones in good to excellent yields. The reaction was successfully achieved when 2-naphthaldehyde instead of benzaldehyde derivatives were used. An aromatic aldehyde containing a nitro substituent took longer reaction time (entry 9 and 13).

As it can be seen in Table 2, the protocol was general and efficient; all reactions proceeded efficiently and the desired products were obtained in good to excellent yields in relatively short reaction times.



Scheme 2. Synthesis of silica vanadic acid (SVA)



R = Phenyl, Naphthyl, Aryl R' = Phenyl, Aryl R'' = Me, Et **1a-n** **1o-q**

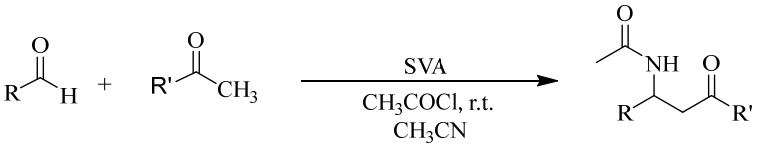
Scheme 3. The synthesis of β-acetamido ketones and esters *via* the condensation reaction between enolizable ketones or alkyl acetoacetates, aldehydes, acetonitrile and acetyl chloride.

Table 1. The condensation of benzaldehyde (1 mmol) with acetophenone (1 mmol), acetyl chloride (0.3 mL) and acetonitrile (3 mL) using different amount of the catalysts.

Entry	Amount of Catalyst (g)	Time (min)	Yield[a] (%)
1	0.01	120	60
2	0.02	95	80
3	0.03	80	88
4	0.04	80	89
5	0.05	80	88

[a]Isolated yield.

Table 2. The synthesis of β-acetamido ketones *via* the condensation of enolizable ketones with aldehydes, acetonitrile and acetyl chloride in presence of silica vanadic acid.



Entry	R	R’	Product	Time (min)	Yield[a] (%)	m.p.(°C)		Ref.
						Found	Reported	
1	C_6H_5	C_6H_5	**a**	80	88	100-102	104-106	[15]
2	C_6H_5	C_6H_4-OMe	**b**	66	93	127-129	130-132	[27]
3	C_6H_4-OMe	C_6H_4-OMe	**c**	70	94	124-127	124-127	[28]
4	$C_{10}H_7$	C_6H_4-OMe	**d**	77	89	108-110	108-110	[28]
5	C_6H_4-Me	C_6H_4-Me	**e**	87	86	118-119	118-119	[28]
6	C_6H_4-Cl	C_6H_4-Me	**f**	90	88	130-132	130-132	[28]
7	$C_{10}H_7$	C_6H_4-Me	**g**	70	92	111-112	112-114	[29]
8	C_6H_5	C_6H_4-NO_2	**h**	78	89	75-76	74-76	[27]
9	C_6H_4-NO_2	C_6H_4-NO_2	**i**	135	84	185-187	187-188	[15]
10	C_6H_4-Cl	C_6H_4-NO_2	**j**	115	86	114-116	116-118	[29]
11	$C_{10}H_7$	C_6H_4-NO_2	**k**	126	89	165-166	165-166	[28]
12	C_6H_5	C_6H_4-Br	**l**	40	95	100-101	98-100	[29]
13	C_6H_4-NO_2	C_6H_4-Br	**m**	140	92	162-163	162-163	[28]
14	$C_{10}H_7$	C_6H_4-Br	**n**	95	88	138-140	138-140	[28]

[a]Isolated yield.

The reaction involving methyl acetoacetate and ethyl acetoacetate led to diastereomeric mixture. However, the products were obtained as a mixture of *syn* and *anti*-isomers favoring *anti*-isomer. The ratio of the diastereomers were determined by ^{1}HNMR spectroscopy (Table 3). The coupling constants between H-2 and H-3 is 6–9 Hz for an anti-isomer and 2–5 Hz for a syn-isomer [30-31].

The major advantages of the present protocol over existing methods can be seen by comparing our results with the most popular recently reported procedures, as shown in Table 3. The reaction of benzaldehyde with acetophenone for the preparation of *N*-(3-oxo-1,3-diphenylpropyl) acetamide (Table 2, entry 1) was chosen as a model reaction and the comparison is in terms of times, conditions and yields of the reaction.

Shorter reaction time was obtained using SVA (Table 4, entry 1) in comparison with the reported of Lewis acid catalysts (Table 4, entry 2-12). So, it can be suggested that V=O centers would be the active sites of the SVA, which participate in the activation of aldehyde or carbonyl groups. SVA not only functioned as a Lewis acid but also as a Bronsted acid in the reaction mechanism. The abovementioned reaction was proceeded in the presence of SVA in comparison with silica sulfuric acid (Table 4, entry 13) under lower reaction temperature. The catalysis results showed that the cooperation of Lewis and Bronsted acid sites in the catalytic procedure can increase the catalytic efficiency of SVA. It has been demonstrated that catalytic systems that contain both Lewis and Bronsted acidity are more beneficial than Lewis or Bronsted acidic catalysts alone.

In another study, to recognize the applicability of our method at large scales, we examined some reactions in scales of 10 mmol. For this purpose, acetophenone or its derivative (10 mmol) was reacted with arylaldehyde (10 mmol), acetyl chloride (3 mL) and acetonitrile (30 mL) in the presence of SVA (0.3 g) at room temperature. The results are summarized in Table 5. As shown in Table 5, the reactions were successfully performed at large scales without significant loss of the yields.

We believe that the silica vanadic acid activates the aldehyde group for nucleophilic attack by creation of hydrogen bond between enolizable ketone and aldehyde until they encounter each other in the right stoichiometry and form the product species [33] (Scheme 4).

4. Conclusions

We have demonstrated a simple procedure for the synthesis of β-acetamido ketones using SVA with Lewis and Brønsted acid sites. High yields, relatively short reaction times, simplicity of operation, low concentration of catalyst, room temperature and easy work-up are some advantages of this protocol.

Acknowledgments

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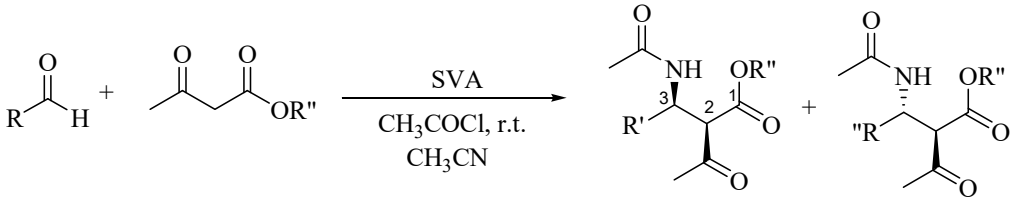
Table 3. The synthesis of β-acetamido esters *via* the condensation of alkyl acetoacetates with aldehydes, acetonitrile and acetyl chloride in presence of SVA.



Entry	R	R”	Time (min)	Yield [a] (%)	Anti /Syn[b]	m.p.(°C)		Ref.
						Found	Reported	
1	C_6H_5	CH_3	70	90	90/10	140-142	140-141	[15]
2	$C_{10}H_7$	CH_3	100	85	57/43	138-139	138-139	[28]
3	$C_{10}H_7$	C_2H_5	155	87	57/43	149-152	149-152	[28]

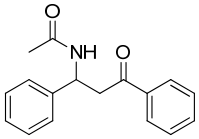
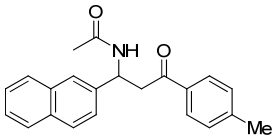
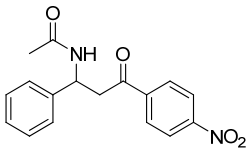
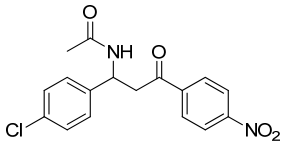
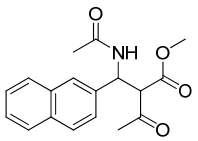
[a]Isolated yield.
[b]Ratio obtained from ^{1}HNMR.

Table 4. Comparison of the results of the reaction of acetophenone with benzaldehyde, acetonitrile and acetyl chloride catalyzed by silica vanadic acid, with those obtained by the reported catalysts.

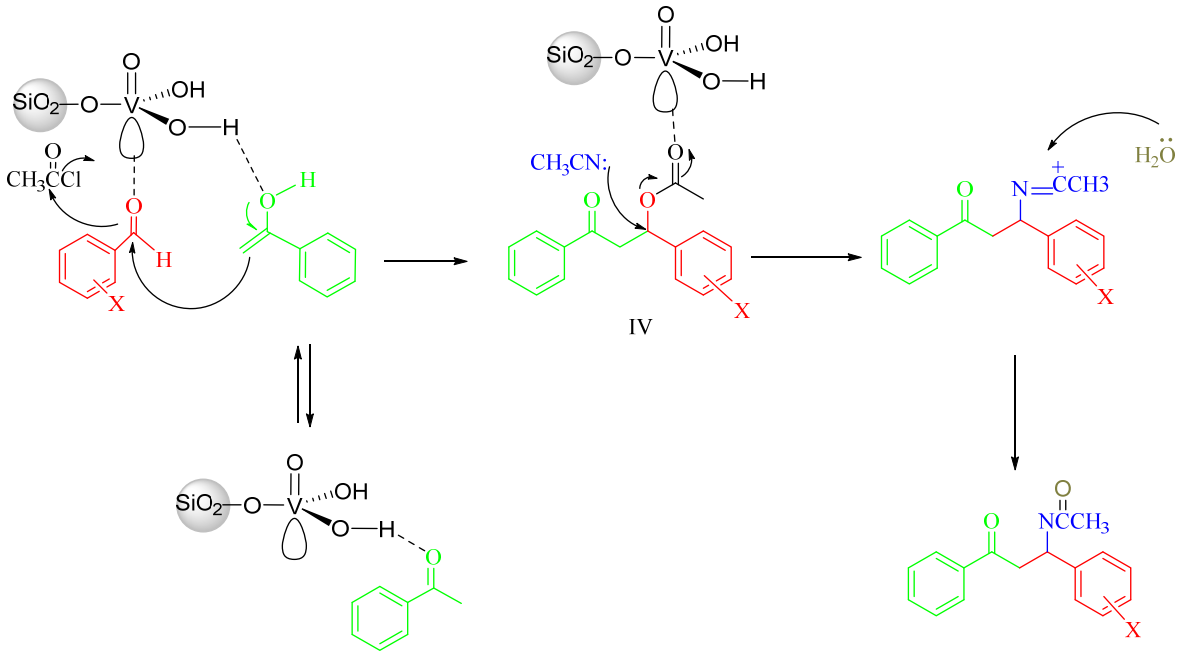
Entry	Catalysis	Reaction conditions	Time (min)	Yield (%)	Ref
1	Silica vanadic acid	r.t.	80	88	This work
2	$SnCl_4/SiO_2$	r.t.	450	82	[32]
3	ZnO	Reflux in MeCN	360	90	[20]
4	$ZrOCl_2.8H_2O$	r.t	300	90	[23]
5	Selectfluor	r.t	240	74	[21]
6	$CeCl_3.7H_2O$	r.t.	420	96	[33]
7	BiOCl	r.t	420	92	[17]
8	$CuSO_4.5H_2O$	r.t	300	92	[34]
9	$FeCl_3.6H_2O$	r.t.	480	88	[35]
10	$Sc(OTf)_3$	r.t.	1800	82	[27]
11	$H_3PW_{12}O_{40}$ [b]	80°C	195	65	[14]
12	$La(OTf)_3$	Reflux in MeCN	180	80	[36]
13	Silica sulfuric acid	80°C	65	91	[19]

[a]Isolated yield.
[b]In this method, trimethylsilyl chloride instead of acetyl chloride has been used.

Table 5. The large scale preparation of some β-acetamido ketones using SVA at room temperature.[a]

Entry	Product	Time (min)	Isolated Yield (%)
1		95	81
2		90	89
3		95	86
4		140	84
5		130	80

[a]Reaction conditions: Enolizable ketones (10 mmol), aldehyde (10 mmol), acetyl chloride (3 mL), acetonitrile (30 mL), SVA (0.3 g), room temperature, stirring.



Scheme 4. The proposed mechanism for the formation of β-acetamido ketone catalyzed silica vanadic acid.

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