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ARTICLE

Synthesis and application of chitosan supported vanadium oxo in the synthesis of 1,4-dihydropyridines and 2,4,6-triarylpyridines *via* anomeric based oxidation

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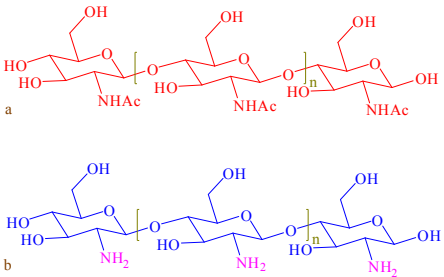
Maliheh Safaiee,*[a] Bahar Ebrahimghasri,[b] Mohammad Ali Zolfigol,*[b] Saeed Baghery,[b] Abbas Khoshnood,*[c] Diego A. Alonso*[c]

Chitosan, as a biopolymer exhibits a strong affinity for complexation with suitable metal ions. Thus, it has been received increased attention for the preparation of stable bioorganic-inorganic hybrid heterogeneous catalysts. Herein, a novel chitosan based vanadium oxo (ChVO) catalyst was prepared and fully characterized by several techniques such as Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), thermal gravimetric analysis (TGA), derivetive thermal gravimetric (DTG), differential thermal analysis (DTA), scanning electron microscopy (SEM), energy dispersive X-ray analysis (EDX), High-resolution transmission electron microscopy (HRTEM), selected area electron diffraction (SAED), X-ray photoelectron spectroscopy (XPS) and inductively coupled plasma mass spectrometry (ICP-MS). The synthesized catalyst has been successfully used as a reusable catalyst in the synthesis of dihydopyridines and triarylpyridines.

Introduction

The heterogeneous catalytic systems are known as essential systems in organic chemistry due to the easy separation, simple recovery and reusability of the catalyst. Therefore immobilization of active catalytic species, mainly transition-metals, on various solid supports is one of the most important processes to improve the efficiency and recycling of catalysts. Vanadium oxo based catalysts have drawn enormous attention due to their versatile role in biological systems[1] and organic synthesis.[2] Therefore immobilization of this bioelement on different supports has been developed to improve its catalytic activities in order to overcome the problems associated with recovery and reusing of expensive homogeneous catalysts and to avoid product contamination. Recently, chitosan (Cs) as a biological polymer is the most abundant natural amino polysaccharide that is usually obtained by deacetylation of chitin. It has attracted significant interest due to its green properties, safety, non-toxicity, biocompatibility, biodegradability, low immunogenicity, stability and ability of chelation (Scheme 1).[3] The insolubility and free NH_2 groups in chitosan make it a wonderful green catalyst and support for using in different areas such as, waste water treatment, pharmaceutical and cosmetic preparations, heavy metal complex, and heterogeneous catalysis.[4-6] On the other hand, growing interest in the application of chitin and chitosan as a support is because of the easy extraction from sea waste, including the exoskeletons of crabs, lobsters, and shrimps.[7] In recent years, chitosan and chitosan-supported transition metal have been reported in a wide range of chemical reactions.[8]



Scheme 1. Chemical structure of chitin (a) and chitosan (b).

Pyridines mainly 2,4,6-triarylpyridines and dihydropyridines as an important class of six-membered nitrogen containing heterocyclic

[a] Department of Medicinal Plants Production, University of Nahavand, Nahavand 6593139565, Iran.
[b] Department of Organic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, Hamedan 6517838683, Iran.
[c] Instituto de Síntesis Orgánica and Departamento de Química Orgánica, Universidad de Alicante, Apdo. 9903080 Alicante, Spain.
*Corresponding Authors: Fax:[b] +988133493009, Phone:[b]+988133493009 e-mail: azalia_s@yahoo.com & msafaiee@nahgu.ac.ir (maliheh Safaiee), zolfi@basu.ac.ir & mzolfigol@yahoo.com, (Mohammad Ali Zolfigol), diego.alonso@ua.es (Diego A. Alonso) and abbas.khoshnood@ua.es (Abbas Khoshnood).

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ring have many applications in medical chemistry and natural products such as NAD nucleotides, pyridoxol (vitamin B6) and pyridine alkaloids.[9] amlodipine, felodipine, isradipine, lacidipine, nicardipine, nitrendipine, nifedipine and nemadipine B are also the commercial drugs which have pyridine and dihydropyridine structures (Figure 1).[10] The oldest and the most known method for the synthesis of 1,4-DHPs and their derivatives was established by Arthur Hantzsch in 1882.[11] In addition to these compounds 2,4,6-triarylpyridine derivatives have been synthesized *via* several methods, including Chichibabin synthesis[12-14] and Kröhnke synthesis.[15-17]

In recent years, attempts to modify the conditions of the synthesis of pyridines[18] and dihydropyridines[19] are still to be continued by using various catalysts mostly consisting of Bronsted or Lewis acids.

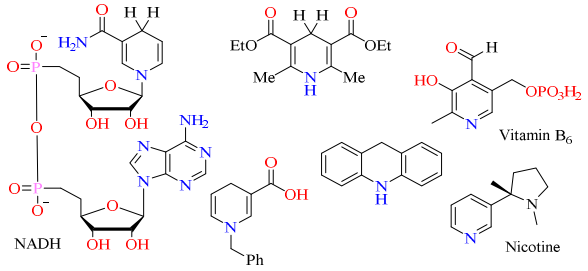
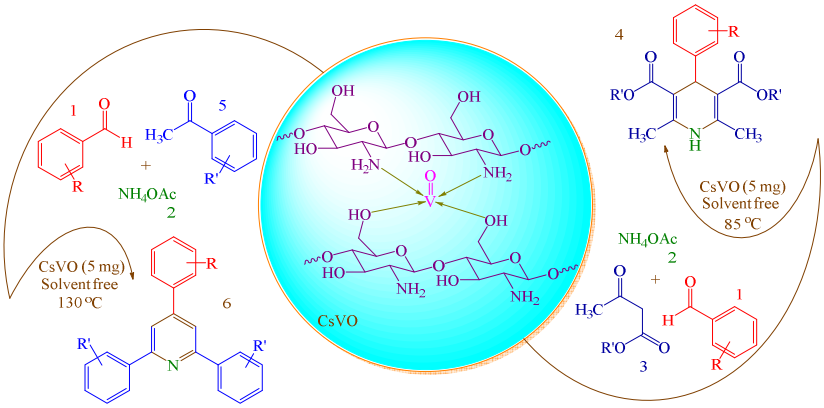


Figure 1. NADH and some typical synthesized NADH analogues or pyridines derivatives.

In continuation of our interest on the application of heterogeneous catalysts and development of anomeric based oxidation,[20,21] herein, we wish to report chitosan as a green biopolymer for synthesis of a novel, simple, effective, inexpensive and recyclable chitosan supported vanadium oxo catalyst and to use it for the synthesis of 1,4-dihydropyridines and 2,4,6-triarylpyridines *via* multicomponent reaction (Scheme 2).



Scheme 2. Catalytic application of chitosan supported oxo-vanadium (ChVO) in the synthesis of 1,4-dihydropyridines and 2,4,6-triarylpyridines.

Results and discussion

Synthesis and characterization of chitosan supported vanadium-oxo (ChVO)

In continuation of the research on the synthesis of the catalyst containing vanadium oxo tags,[22] ChVO was synthesized *via* simple and green method by refluxing chitosan and vanadium pentoxide in water. The structure of ChVO was approved and fully characterized using FT-IR, XRD, SEM, EDX, ICP-MS and TGA analysis techniques.

In order to confirm the surface modification of chitosan, the FTIR spectra of the V_2O_5, pure chitosan and ChVO are shown in Figure 2. The main peaks observed in the FTIR spectra of pure chitosan are:

(a) A band about 3259-3685 cm^{-1} is related to the -OH and -NH_2 stretching.

(b) The band at 2923 and 2868 cm^{-1} is related to the symmetric and asymmetric stretching of C-H.

(c) The signal at 1588 cm^{-1} was assigned to -NH_2 bending.

(d) The bands at 1386 and 1088 cm^{-1} are assigned to C-N and C-O stretching respectively.[23]

In the case of the V_2O_5, the strong band observed at 1027 cm^{-1} is related to the V=O stretching, The peaks at approximately 525 and 816 cm^{-1} revealed the V–O–V symmetric and asymmetric stretching modes.

The FT-IR spectra of VO immobilized chitosan shows similar to the pure chitosan with a slight difference. In pure chitosan, only one very strong and broad band (presence of relatively hydrogen bonds) assignable to the O–H and N–H stretching can be identified. In the catalyst, a weak splitting of this broad band can be observed. More importantly, the band at the 1588 assigned to -NH_2 in chitosan was changed in the catalyst which indicates a donation of electron density from the -NH_2 to the metal center.

The EDX data of ChVO confirms the presence of the anticipated elements in the structure of the catalyst: carbon, nitrogen, oxygen and vanadium (Figure 3). The vanadium content of ChVO was measured *via* ICP-MS, which gives a value of 9.4833 % (w/w).

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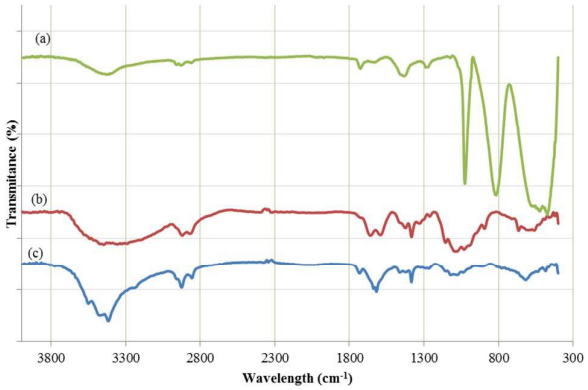


Figure 2. FT-IR spectra: (a) V_2O_5; (b) Chitosan (c) ChVO.

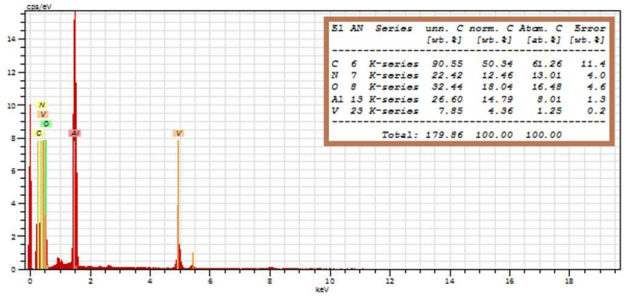
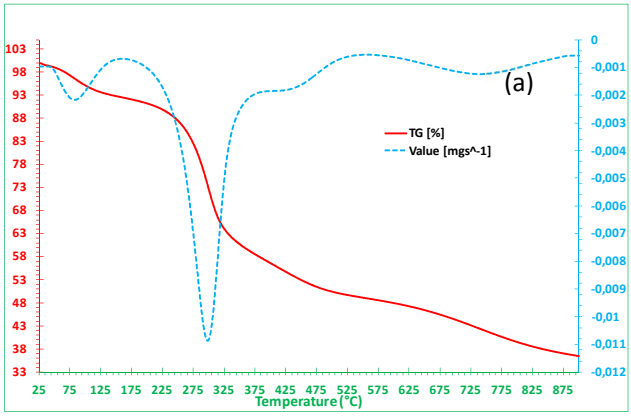


Figure 3. EDX spectrum of ChVO.

Another indication of bond formation between vanadium oxo and chitosan can be inferred from TGA. Furthermore, thermal stability of the catalyst was given by TG and DTG (Figure 4). In the TG curve of the catalyst, the weight loss at temperatures below 110 °C is due to the removal of physically adsorbed solvent and surface hydroxyl groups. According to TG and DTG diagrams, weight loss of the catalyst occurred in one step, after 225 °C which was related to VO functionalized chitosan. This study showed that the catalyst can be used at temperatures below 225 °C.



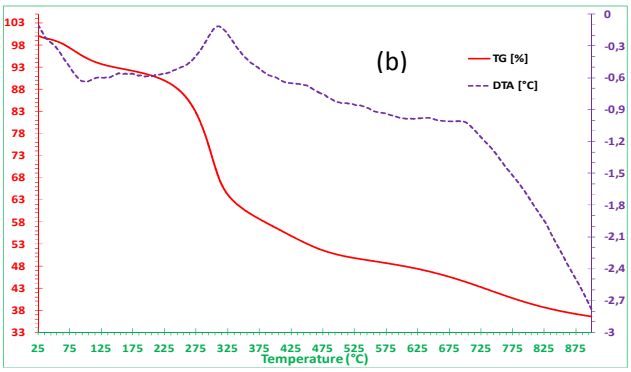
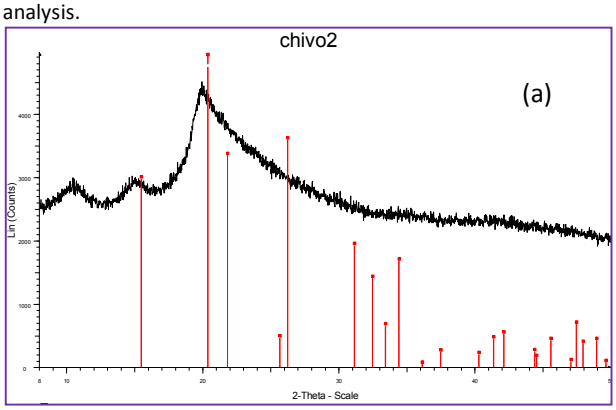


Figure 4. Thermal gravimetric analysis [TGA/DTG] (a) and inlet [TGA/DTA] (b) of ChVO

The particle size, shape and the morphology of the catalyst were studied using XRD and SEM (Figures 5 and 6). The XRD pattern of the catalyst exhibited that the catalyst nature was non-crystalline and amorphous at 2θ = 18.5–30.5 (Figure 5). In order to explore the elemental composition of the catalyst ChVO, SEM images and WDX elemental maps were done and shown in Figure 5. Presence of V, N, O, and C elements in the catalyst are shown *via* WDX analysis.



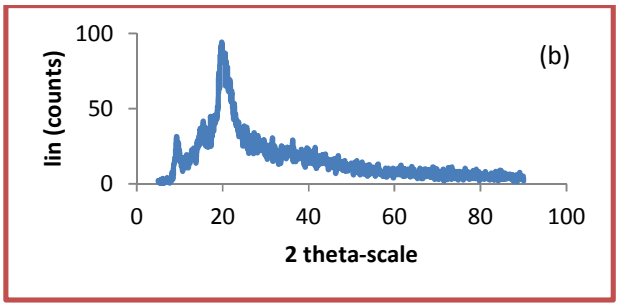


Figure 5. XRD diffraction pattern of ChVO (black). V_2O_5 standard orthorhombic signals [01-075-0457] (red lines) [a], chitosan (b).

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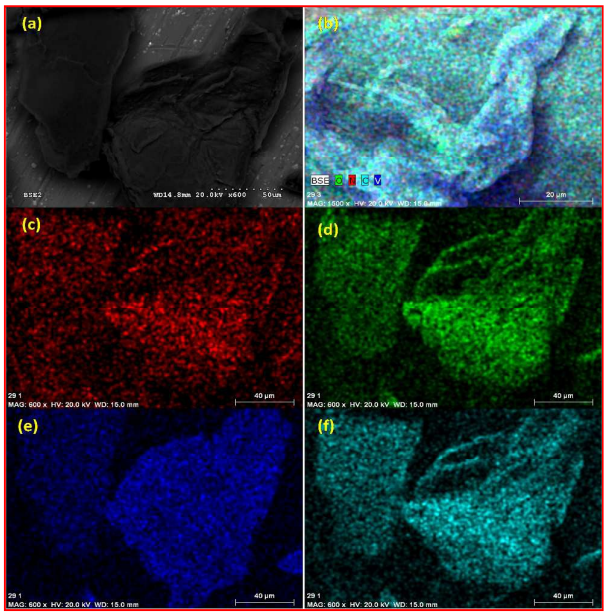

Figure 6. SEM image (a) and WDX elemental mapping images of ChVO (b) nitrogen (c), oxygen (d), vanadium (e) and carbon (f).

Furthermore, high resolution transmission electron microscopy (HRTEM) images with its selected area electron diffraction (SAED) of the ChVO were illustrated to obtain more detailed structural information and crystallite information of the catalyst in Figure 7 a-c. It is observed that all coordinated vanadium nanoparticles well dispersed, which are highly uniformed by chitosan as efficient supporting donating ligand. Moreover, as shown from the SAED pattern image in Figure 7c, amorphous coating chitosan covered over the crystalline vanadium oxide which presented a multi crystalline system pattern. Moreover, the diffraction pattern shows prominent rings with inter planar spacing values of 5.43, 4.42, 3.80 and 3.06 Å corresponding to (200), (010), (110) and (101) planes respectively for vanadium oxide (JCPDS no. 01-075-0457).

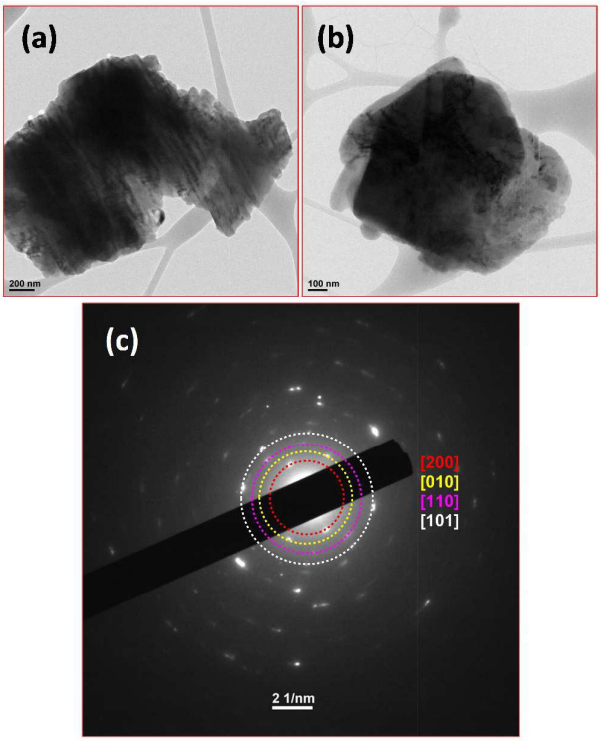

Figure 7. HRTEM images (a, b) and SAED of the ChVO (c)

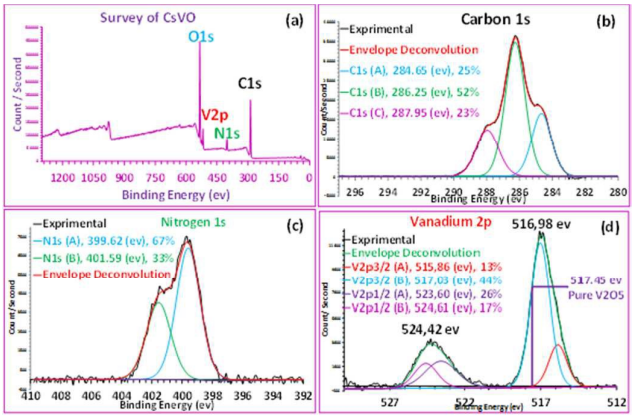

Figure 8: XPS spectra of (a) survey and High-resolution XPS spectra (b) C1s; (c) N1s; (d) V2p of catalyst ChVO

Additional investigation for surface composition and the oxidation states of the vanadium (V) at ChVO was performed by using X-ray photoelectron spectroscopy (XPS) measurements (Figure 8)[24-26,22h]. As expected from starting materials, the peaks corresponding to C1s, O1s and N1s from chitosan and V2p from V_2O_5 were clearly seen in the XPS survey spectrum of the final catalyst ChVO with atomic percentages of 54, 36, 7 and 3, respectively (Figure 8a). For the first high resolution XPS, C1s de-convolution as a reference element was studied showing three peaks at 284.6 $(CH_2)_n$, 286.2 (C–NH_2, C–OH) and 287.9 eV O–C–O or (C–O–V , C–N–V) with a relative area of (1:2:1), respectively (Figure 8b)[24,27]. Moreover, the N1s XPS spectrum of ChVO (Figure 8c) was de-convoluted into two peaks at 399.62 and 401.59 eV, revealing the existence of non-coordinated C–NH_2 and

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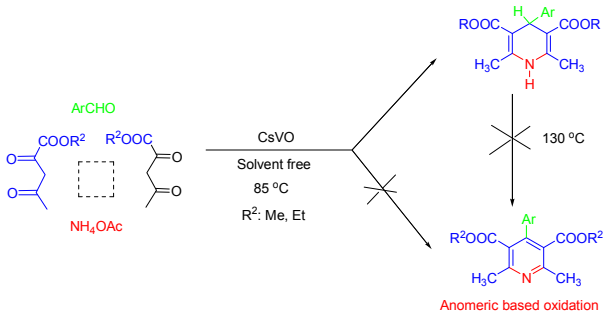
coordinated (C–$N^{+\delta}$…$V^{-\delta}$) moieties, respectively, with a relative area of (1:0.5). These XPS results clearly demonstrated the presence of free (non-coordinated to V) and coordinated chitosan in a 2:1 ratio. Furthermore, these results clearly approved that the nitrogen and oxygen sites of the chitosan moieties (-NH_2, -OH) are coordinated to the central Vanadium metals in the catalyst.

On the other hand, as shown in Tables 7 and 8, the catalytic activity of ChVO is completely different from the starting V_2O_5/chitosan system. Therefore, the high-resolution XPS spectrum of V2p could be used as a potential evidence of the oxidation state of the ChVO catalyst. As shown in (Figure 8d), the V2p spectrum comprises two singlet binding energies located at approximately 516.98 eV ($2p_{3/2}$) and 524.42 eV ($2p_{1/2}$) with a 7.4 eV band gap distance, which is used as atypical bonding energy reference for Vanadium 2p. Each V2p peak can be de-convoluted and fitted into the two different peaks located at 515.86, 517.03 eV, corresponding to ($2p_{3/2}$) and 523.60, 524.61 eV, which corresponded to ($2p_{1/2}$) level. Moreover, the binding energy of vanadium at ChVO was a broad, non-symmetrical single peak shifted at 516.98 eV, which could be fitted and de-convoluted into two different peaks located at 517.03 and 515.86 eV with a relative area of (4:1). This contrasts with the single, sharp, symmetrical and more precise V2$p_{3/2}$ peak of V_2O_5, which appears at 517.45 eV.[24] The negative shift of the V2$p_{3/2}$ binding energy in the catalyst suggests the presence of electron-donating coordination and/or alcohol-derived reducing moieties (–$O^{+\delta}$…$V^{-\delta}$ and –$N^{+\delta}$…$V^{-\delta}$).[28] Finally, the results from the more intense and precise V2$p_{3/2}$ peak, clearly indicated the absence of non-coordinated V_2O_5 and a partial reduction of the V(V) to V(IV), being the former oxidation state at 517.03 eV predominant over the second at 515.86 eV.

Catalytic activity of ChVO.

a. Synthesis of 1,4-dihydropyridines.

In continuation of our investigation on the synthesis of 1,4-dihydropyridines[19], we decided to use described catalyst for *in situ* synthesis of 1,4-dihydropyridines and their aromatization to the corresponding pyridines *via* anomeric based oxidation. Recently we have introduced a new terminology entitled "anomeric based oxidation" (ABO) for the final step of the aromatization of a good range of heterocyclic compounds (Schemes 1-7, SI)[21]. We think that above-mentioned catalyst (ChVO) is suitable for this idea. Therefore, after characterizing the catalyst, in order to investigate the proficiency of the catalyst, we used it in the synthesis of 1,4-dihydropyridines. For the synthesis of dihydropyridines, aldehyde, ethyl or methyl acetoacetate and ammonium acetate were applied to react with each other in the presence of described new catalyst (Scheme 3).



Scheme 3. Synthesis of 1,4-dihydropyridines in the presence of ChVO.

We performed the reaction under different conditions to achieve the best condition. As it can be seen from Table 1, the best temperature is 85 °C and it can be understood that less amount of catalyst will cause more yield in the product. Raising the reaction to 130 °C does not change the result and the corresponding pyridine was not observed. We also performed the reaction in different solvents (Table 2). The results of the reaction in both ethanol and solvent-free condition are the same. Therefore, according to the optimized reaction conditions, synthesis of 1,4-dihydropyridines was done using different electron-donating and electron-withdrawing aromatic aldehydes. The results are represented in Table 3. In view of these results, we selected the optimized reaction conditions to determine the efficiency of this catalyst. A wide range of aromatic and heteroaromatic aldehydes were subjected to react with ethyl or methyl acetoacetate and ammonium acetate in the presence of the catalyst. The results are shown in Table 3. As we expect the aldehyde substrates containing electron donor groups participated in reaction as well as aldehydes containing electron withdrawing groups. The cases like furan-2-carbaldehyde and thiophene-2-carbaldehyde showed excellent yields that probably could relate with less steric hindrance.

Table 1. Result of the amount of catalyst and temperature on the condensation reaction between 4-chlorobenzaldehyde (2 mmol), ethyl acetoacetate (4 mmol) and ammonium acetate under solvent-free condition.

Entry	Temperature (°C)	Amount of catalyst (mg)	Amount of ammonium acetate (mmol)	Reaction time (min)	Isolated yield (%)
1	25	5	3	60	Trace
2	50	5	3	60	35
3	85	5	3	45	89
4	85	5	2	45	84
5	85	5	4	45	89
6	85	10	3	55	82
7	85	20	3	60	71
8	85	30	3	60	62
9	100	5	3	45	89
10	130[a]	5	3		

[a]Only 1,4-dihydropyridine was produced and the corresponding pyridine was not observed.

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Table 2. The effect of different solvents on the reaction between 4-chlorobenzaldehyde (2 mmol), ethyl acetoacetate (4 mmol), ammonium acetate (3 mmol) catalyzed by ChVO (5 mg) under reflux condition.

Entry	Solvent	Reaction time (min)	Isolated yield (%)
1	Solvent-free[a]	45	89
1	Ethylacetate	60	86
2	*n*-Hexane	90	55
3	Dichloromethane	180	Trace
4	Ethanol	45	89
5	Acetonitrile	60	79
6	Water	120	Trace

[a]at 85 °C.

Table 3. Synthesis of 1,4-dihydropyridines.[a]

Entry	R	R′	Reaction time(min)	Isolated yield(%)	M.p (°C) [Lit][Ref]
1	C_6H_5	Et	55	89	156-158 [158-160] [29]
2	4-Cl-C_6H_4	Et	45	89	146-148 [144-145] [29]
3	2,4-$(Cl)_2$-C_6H_3	Et	45	89	148-151 [152-154] [29]
4	2,4-$(F)_2$-C_6H_4	Et	50	84	133-136
5	4-Br-C_6H_4	Et	40	94	163-166 [162-164] [29]
6	4-NO_2-C_6H_4	Et	40	93	129-132 [130-132] [29]
7	3-NO_2-C_6H_4	Et	40	91	164-167 [166-168] [29]
8	4-CN-C_6H_4	Et	50	93	159-162 [165-167] [30]
9	4-OH-C_6H_4	Et	55	81	221-224 [226-228] [31]
10	4-$N(Me)_2$-C_6H_4	Et	55	88	154-157 [200-202] [32]
11	3-OEt-4-OH-C_6H_3	Et	50	88	161-163
12	4-OMe-C_6H_4	Et	45	86	158-160 [154-155] [29]
13	2-Thienyl	Et	20	96	169-171 [171-172] [29]
14	2-Furyl	Et	20	96	164-167 [160-161] [29]
15	4-Cl-C_6H_4	Me	40	92	190-194 [196-198] [**29**]
16	3,4-$(F)_2$-C_6H_3	Me	45	92	160-163 [165-167] [**33**]
17	4-CN-C_6H_4	Me	40	90	233-237 [225-227] [30]
18	4-CHO-C_6H_4	Me	50	85	More than 310 [More than 300] [34]
19	4-$N(Me)_2$-C_6H_4	Me	50	88	193-196 [191-193] [**32**]
20	4-Me-C_6H_4	Me	55	86	168-171 [175-177] [29]

[a]Reaction conditions: aldehyde (2 mmol), ethyl acetoacetate or methyl acetoacetate (4 mmol), ammonium acetate (3 mmol), ChVO (5 mg) at 85 °C under solvent-free condition.

The mechanism for the preparation of 1,4-dihydropyridines using ChVO as a catalyst was suggested in scheme 4. First, ChVO activates the carbonyl functional group of aldehyde for the nucleophilic addition of enol form of *β*-ketoesters 7 on it to form the corresponding Knoevenagel intermediate (8). Ammonia was prepared *in situ* of ammonium acetate 2 and attacks the second equivalent of the *β*-ketoester and produces the intermediate 10. Further condensation between these two intermediates 8 and 10 gives the dihydropyridines 4.

b. Synthesis of 2,4,6-triarylpyridines.

We decided to carry out another reaction in order to make sure that our catalyst has a good efficiency. So, we chose to synthesize 2,4,6-triarylpyridines using the bio heterogeneous catalyst (Scheme 5). Initially, to optimize the reaction conditions, the condensation reaction of 4-chlorobenzaldehyde, 4-methoxyacetophenone and ammonium acetate was used as a model, and was conducted under different reaction conditions by varying the reaction parameters such as temperature and amount of catalyst. It is clear that the best condition for carrying out the reaction is under solvent-free with temperature of 130 °C using 5 mg of catalyst (Tables 4 and 5). As shown in Table 6, a wide range of aromatic aldehydes underwent electrophilic substitution reaction with acetophenone derivatives and ammonium acetate to afford various substituted 2,4,6-triarylpyridines in good to excellent yields.

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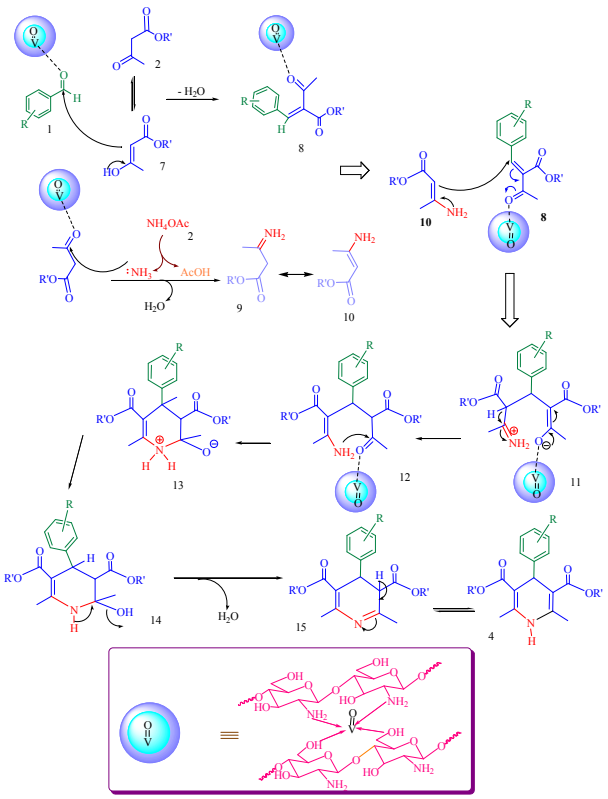
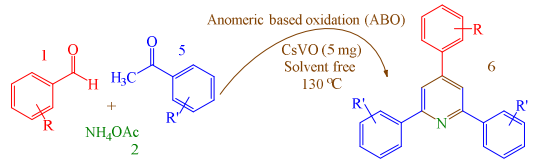


Scheme 4. The proposed mechanism for the synthesis of 1,4,dihydropyridines using ChVO as a catalyst.



Scheme 5. Synthesis of 2,4,6-triarylpyridines in the presence of ChVO.

The proposed catalytic mechanism is suggested in Scheme 6. Firstly acetophenone is turned into its enol form by ChVO, which affords nucleophilic addition to the carbonyl groups that are activated by the catalyst. Then the second molecule of enol as a nucleophilic attacks the intermediate 17 to give 18. Then, after nucleophilic attack of ammonia (prepared *in situ* of ammonium acetate 2) to intermediate 18 which is activated by the catalyst, intermediate 19 will gained and then it is followed by cyclization and tautomerization to 20. We believed that, this step might be progressed through uncommon hydride transfer named anomeric based oxidation (ABO). Very recently, our group proposed an anomeric based oxidation for the final step of many reactions that are mentioned in supporting information (Schemes 1-7, SI).[21] In this case the nitrogen lone pair and phenyl groups release the electron into the anti-bonding of C–H (δ* C–H orbital) so that the allylic hydrogen of intermediate **19** can be broken by promoting rule of described catalyst. Whenever in the synthesis of the dihydropyridines **4** the temperature of reaction rises to 130°C (Scheme 5) similar to the triarylpyridines synthesis, the anomeric based oxidation reaction does not take place. Two following reasons may be present for clearing explanation of why oxidation occurs in one case, but not in the other one. First the methyl groups of 1,4-dihydropyridines **4** could not act alike of phenyl moieties on intermediate **19** as resonance donating groups. Second, the nitrogen lone pair of 1,4-dihydropyridines **4** prefers to resonance with its carbonyl functional groups instead of anti-bonding of allylic C–H (δ* C–H orbital).

The recyclability of the catalyst was also investigated. The catalyst was recovered by filtration, washed with ethyl acetate, dried and reused for a further runs. The results are shown in Figure 7. In this regard for investigating the reusability of our new prepared catalyst in the synthesis of 4-(4-chlorophenyl)-2,6-bis(4-methoxyphenyl)pyridine, we performed the model reaction using 4 mmol 4-chlorobenzaldehyde, 8 mmol 4-methoxyacetophenone and 20 mmol ammonium acetate in the presence of 20 mg catalyst. The catalyst was recycled three times with just a marginal loss of its activity. Also the catalyst was recycled three times with just an insignificant loss of its activity in the synthesis of diethyl-4-(4-chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate *via* the reaction between 4 mmol 4-chlorobenzaldehyde, 8 mmol 4-methoxyacetophenone and 20 mmol ammonium acetate using 20 mg catalyst.

Table 4. Result of the amount of catalyst and temperature on the condensation reaction between 4-chlorobenzaldehyde (1 mmol), 4-methoxyacetophenone (2 mmol) and ammonium acetate under solvent-free condition.

Entry	Temperature (°C)	Amount of catalyst (mg)	Amount of ammonium acetate (mmol)	Reaction time (min)	Isolated yield (%)
1	90	5	5	90	47
2	110	5	5	70	65
3	130	-	5	110	38
4	130	5	5	55	88
5	130	10	5	55	81
6	130	20	5	60	72
7	130	5	1	70	71
8	130	5	3	55	82
9	150	5	5	55	88

Table 5. Effect of different solvents on the condensation reaction between 4-chlorobenzaldehyde (1 mmol), 4-methoxyacetophenone (2 mmol) and ammonium acetate (5 mmol) catalyzed by ChVO (5 mg) under reflux condition.

Entry	Solvent	Reaction time (min)	Isolated yield (%)
1	Solvent-free[a]	55	88
2	Ethanol	60	48
3	Water	120	_
4	*n*-Hexane	120	_

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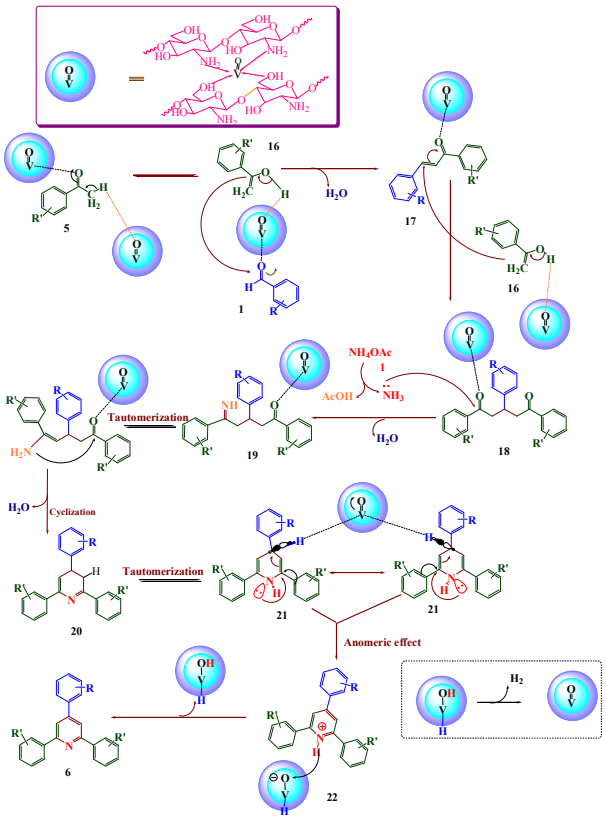
5	Ethylacetate	60	43

[a]at 130 °C.

Table 6. Synthesis of 2,4,6-triarylpyridines.[a]

Entry	R	R′	Reaction time (min)	Isolated yield (%)	M.p (°C) [Lit][Ref]
1	C_6H_5	H	65	79	134-136 [134-135][35]
2	C_6H_5	Cl	60	80	180-182 [186-187][35]
3	4-OMe-C_6H_4	Cl	75	67	188-190 [193-194][35]
4	4-OMe-C_6H_4	OMe	60	80	125-127 [134-135][35]
5	3-OH-C_6H_5	Cl	65	87	235-238
6	4-N(Me)$_2$-C_6H_4	OMe	60	81	131-133 [149-150][35]
7	3-NO_2-C_6H_4	Cl	70	88	234-236 [230-232][35]
8	3-NO_2-C_6H_4	OMe	55	81	88-90
9	4-Cl-C_6H_4	Cl	55	84	265-267 [269-270][35]
10	4-Cl-C_6H_4	OMe	55	88	112-113 [110-112][21b]
11	3,4-(F)$_2$-C_6H_3	H	75	62	176-178
12	3,4-(F)$_2$-C_6H_3	OMe	60	53	131-133
13	3,4-(F)$_2$-C_6H_3	Cl	75	83	250-252
14	3,5-(F)$_2$-C_6H_3	Cl	65	87	236-238
15	4-Br-C_6H_4	OMe	55	83	151-153 [165-166][36]

[a]Reaction conditions: aldehyde (1 mmol), acetophenone (2 mmol), ammonium acetate (5mmol), ChVO (5 mg) at 130 °C under solvent-free condition.



Scheme 6. The proposed mechanism for the synthesis of 2,4,6-triarylpyridines using ChVO as a catalyst.

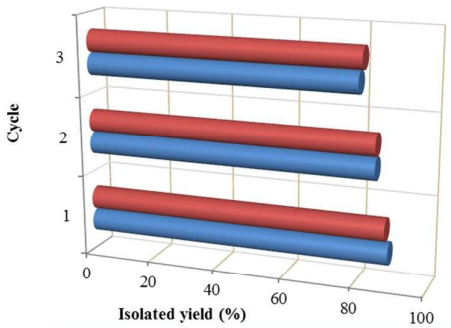
The comparison between the efficiency of ChVO and catalyst's components for investigating the catalyst activity in the synthesis of 2,4,6-triarylpyridines and 1,4-dihydropyridine derivatives, using condensation reaction of 4-chlorobenzaldehyde, 4-methoxyacetophenone and ammonium acetate [in the synthesis of 4-(4-chlorophenyl)-2,6-bis(4-methoxyphenyl)pyridine] and 4-chlorobenzaldehyde, ethyl acetoacetate and ammonium acetate [in the synthesis of diethyl 4-(4-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate] are presented in Tables 7 and 8. As it shown in Tables 8 and 9, our catalyst acts better than chitosan and V_2O_5 in the synthesis of 4-(4-chlorophenyl)-2,6-bis(4-methoxyphenyl)pyridine.

The hot-filtration test was also carried out by stopping the reaction at half-conversion and then, the catalyst is separated without cooling the solution. After the removal of the catalyst, the solution was heated at 130°C for 1hour and no further conversion was observed after 1 h. ICP spectroscopy of the catalyst after three run represented a value of 1.0521% (w/w).

ICP spectroscopy was applied for determining of the amount of vanadium in the recycled catalyst. Studies of ICP obtained data shows that the amount of vanadium was decreased in the recycled catalyst from 45.3 mg L^{-1} (in the first run of recycled catalyst) to 18 mg L^{-1} in the third run (which represents leaching of catalyst is decreased in the course of recycling process) (Table 7).

Table 7. ICP analysis for determination of vanadium in the recycled catalyst.

Number of recovery	Amount of V (mg L^{-1})
1	45.3
2	32.7
3	18.0



	1	2	3
Pyridine	88	85	81
Dihydropyridine	89	85	80

Figure 7. Recyclability of ChVO.

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Table 8. Condensation reaction of 1 mmol 4-chlorobenzaldehyde, 2 mmol 4-methoxyacetophenone and 5 mmol ammonium acetate in the presence of chitosan, V_2O_5 and CHVO.

Catalyst	Time(min)	Yield(%)
Chitosan	110	42
V_2O_5	110	33
ChVO	55	88

Table 9. Condensation reaction of 2 mmol 4-chlorobenzaldehyde, 4 mmol ethyl acetoacetate and 3 mmol **ammonium acetate** in the presence of chitosan, V_2O_5 and ChVO.

Catalyst	Time(min)	Yield(%)
Chitosan	45	89
V_2O_5	90	51
ChVO	45	89

Experimental

General

All chemicals and solvents used were of reagent grade and purchased from Sigma-Aldrich, Fluka, Merck and Acros Organics. All reagents were used without any further purification. TLC analysis was performed on UV-active aluminiumbacked F254 silica gel plates. Melting points were measured with a Thermo Scientific apparatus and they were uncorrected. Centrifugation procedures were performed with an Anke TDL80-2B. Fourier transform infrared (FT-IR) spectra were recorded with a PerkinElmer FT-IR 17259 spectrometer using KBr discs. ^{1}H NMR (400 or 300 MHz) spectra were obtained with Bruker Avance 400 and 300 NMR spectrometers, respectively, in proton coupled mode using deuterated dimethylsulfoxide (DMSO) as a solvent, unless otherwise stated. ^{13}C NMR (101 MHz) spectra were acquired with a Bruker Avance 400 NMR spectrometer in proton decoupled mode at 20 °C in deuterated DMSO as solvent, unless otherwise stated. Chemical shifts are given in parts per million and the coupling constants (J) in hertz. Data for ^{1}HNMR are reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad), coupling constant (Hz) and integration. Thermogravimetric analysis (TGA) was carried out with a Mettler Toledo apparatus (models TGA/SDTA851 and /SF/1100 TG/DTA). TGA was performed under a nitrogen atmosphere at 25 °C and using a heating rate of 20 °C min^{-1} up to 700 °C. Samples were prepared by drop-casting dispersed particles onto a 200-mesh copper grid coated with a holey carbon film. Scanning electron microscopy (SEM) studies were performed using a Hitachi S3000 N, equipped with an X-ray detector (Bruker XFlash 3001) for microanalysis (energy-dispersive X-ray, EDX) and mapping (wavelength-dispersive X-ray, WDX). X-ray diffraction (XRD) analyses were performed using a Bruker D8-Advance apparatus using a monochromatized Cu Kα (λ = 0.154 nm) X-ray source in the range 5° < 2θ < 60°. XRD patterns of chitosan was performed on a APD 2000, Ital structure with Cu K_ radiation (k = 0.1542 nm) operating at 50 kV and 20 mA in a 2 h range of 10‾70° with step size 0.01° and time step 1.0 s to assess the crystallinity of the catalyst. Inductively coupled plasma mass spectrometry (ICP-MS) was performed with an Agilent 7700x apparatus equipped with HMI (high matrix introduction) and the ICP of hot filtration was done by Varian, ICP-OES 730-ES.

General procedure for the preparation of ChVO

In a round-bottomed flask (100 mL), chitosan (1.7 g) and vanadium pentaoxide (0.33 g) were refluxed in water for 24 h. The resulting black catalyst was then separated by filtration and washed three times with hot distilled water and twice with diethyl ether and finally dried under vacuum at 80 ° C and fully characterized.

General procedure for the synthesis of 1,4-dihydropyridines

A mixture of aldehyde (2 mmol), *ß*-ketoser (4 mmol) and ammonium acetate (3 mmol) was poured into a round-bottomed flask and ChVO (5 mg) was added to them under solvent-free condition at 85 °C for a suitable time. The reaction progress was studied using thin layer chromatography (*n*-hexane:ethyl acetate, 3:7). After the reaction was completed, the mixture was cooled to ambient temperature. In order to isolate the catalyst from the reaction medium, 10 ml of hot ethyl acetate was added until the reaction mixture was completely dissolved in the solvent. Then, by filtering, the heterogeneous catalyst was removed from the reaction mixture and used for similar reactions. After evaporation of the solvent, for purification, the crude product was washed twice with *n*-hexane and then recrystallized from 1:10 ethanol/water.

General procedure for the synthesis of 2,4,6-triarylpyridines

To the mixture of aromatic aldehydes (1 mmol), acetophenone derivatives (2 mmol) and ammonium acetate (5 mmol) in a round bottom flask, was added ChVO (5 mg) as a heterogeneous catalyst and the resulting mixture was stirred magnetically under solvent-free condition at 130 °C in an oil bath for the suitable time (Table 6). The progress of the reaction was studied using TLC (*n*-hexane:ethyl acetate, 4:15). After the reaction was completed, the mixture was cooled to ambient temperature. In order to isolate the catalyst from the reaction mixture, 10 ml of hot ethanol was added to it until the reaction mixture was completely dissolved in the solvent. The catalyst was filtered and carefully washed with ethanol and dried under vacuum and then it was used for the next run of the model reaction. The pure product was also recrystallized from the ethanol.

Conclusions

In conclusion, VO supported chitosan as has been prepared and fully characterized. The present method is operationally simple, clean and efficient procedure for the synthesis of 1,4-dihydopyridines and triarylpyridines using a catalytic amount of ChVO. In addition simple stable and green synthesis of catalyst, low cost, easy availability, recyclability, short reaction times, and solvent-free condition of reaction make this method practical for the synthesis of pyridines and dihydropyridines. We think that the obtained results from this research will support the idea of rational design, synthesis and applications of new and tasked-specific bioorganic-inorganic hybrid catalysts and catalytic systems.

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Graphical abstract

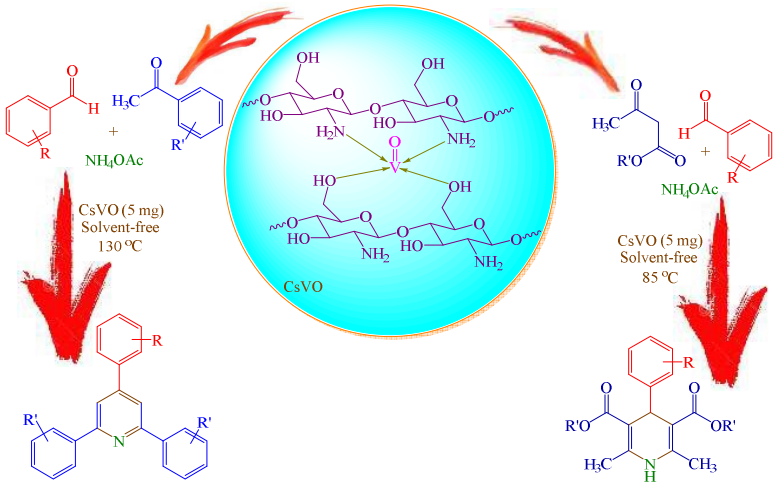
Synthesis and application of chitosan supported vanadium oxo in the synthesis of 1,4-dihydropyridines and 2,4,6-triarylpyridines *via* anomeric based oxidation

Maliheh Safaiee,*[a] Bahar Ebrahimghasri,[b] Mohammad Ali Zolfigol,*[b] Saeed Baghery,[b] Abbas Khoshnood,*[c] Diego A. Alonso*[c]

[a.] *Department of Medicinal Plants Production, University of Nahavand, Nahavand 6593139565, Iran.*

[b.] *Department of Organic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, Hamedan 6517838683, Iran.*

[c.] *Instituto de Síntesis Orgánica and Departamento de Química Orgánica,Universidad de Alicante, Apdo. 9903080 Alicante, Spain.*



1,4-Dihydropyridines and 2,4,6-triarylpyridines were synthesized *via* anomeric based oxidation using chitosan supported vanadium oxo.