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Vanadatesulfuric Acid Nanorod Particles-catalyzed Novel and eco-benign one-pot Synthesis of Polyhydroquinoline Derivatives under Solvent-free Conditions

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ABSTRACT

A novel and green approach for efficient and rapid synthesis of biologically active polyhydroquinoline derivatives via unsymmetric Hantzsch reaction using nanorods Vanadatesulfuric acid (VSA NRs) as a new and recyclable catalyst under solvent-free conditions was reported. The catalyst was characterized by FT-IR, XRD, XRF and TEM analysis. The present method offers several advantages such as simple procedure, short reaction time, high yields, simple workup, reusability of the catalyst and simple purification of the products.

Key words: Aldehyde, 1,3-cyclohexanediones, heterogeneous catalysis, polyhydroquinoline, vanadatesulfuric acid.

INTRODUCTION

In pharmaceutical view, heterocycles are of superior importance in the discovery and design of new compounds[1]. Recently, an increasing attention has been focused toward the multicomponent synthesis of 1,4-dihydropyridyl compounds due to their broad range of biological activities[2]. 1,4-dihydropyridines as analogues of NADH coenzymes, such as nifedipine, nicardipine, amlodipine, and other related derivatives, are widely used as calcium channel blockers for the treatment of cardiovascular disorder including angina, hypertension and cardiac arrhythmias[3]. 1,4-Dihydropyridines are calcium antagonists[4], antitubercular agents[5], and neuropeptide Y Y1 receptor antagonists[6]. They possess neuroprotective[7], platelet antiaggregation[8], antidiabetic activities[9] cerebral antischemic activity in the treatment of Alzheimer's disease, and chemosensitizer in tumor therapy[10]. Also quinolines are very important compounds. Members of this group are being used as anti-inflammatory, antimalarial, antibacterial, antiasthamatic, and tyrosine kinase inhibiting agents[11].

These examples clearly demonstrate the remarkable potential of novel DHP family as a source of valuable drug candidates. Thus, the synthesis of this heterocyclic nucleus is of great importance.

More than a century ago the synthesis of 1,4-dihydropyridines by classical Hantzsch

method[12], a one-pot condensation of an aldehyde with alkyl acetoacetate and ammonia, was presented. However, the yields of these compounds obtained by the Hantzsch synthesis are generally low.

Therefore, numerous promotions, such as using ionic liquids[13,14], microwaves[15-17], grinding[18], silica-supported acids[19,20], L-proline[21], HY-zeolite[22], Bu_4NHSO_4[23], boronic acids[24,25], TMSCl–NaI[26], ceric ammonium nitrate[27,28], metal triflates[29,30], *p*-TSA[31], and baker's yeast[32,33] have been developed. However, many of these methods still suffer from several limitations, such as unsatisfactory yield, use of environmentally suspected organic solvents, long reaction time, high temperature, and using expensive and non reusable catalysts. Therefore, investigation for improved reaction conditions for synthesis of polyhydroquinolines using novel and reusable catalysts under solvent-free conditions is still desired.

Multicomponent reactions as an efficient and dominant tool in modern synthetic organic chemistry allow the facile creation of several new bonds in a one-pot reaction. This reduces the reaction time, and saves money, energy, and raw materials[34]. Therefore, research in industry and academic has increasingly emphasized the use of multicomponent reactions as well as domino reaction sequences for a wide range of products[35].

Solid acid catalysts with lower toxicity, higher stability and recyclability play a prominent role in organic synthesis under heterogeneous conditions. Solid acids have many advantages such as ease of handling, decreasing reactor and plant corrosion problems, and environmentally safe disposal[36,37].

It is well known in the protocol of green chemistry that its main objective is to perform reactions under solventless conditions using heterogeneous catalysts, in order to generate environmentally friendly chemical transformations[38]. In addition, it is important to note that an ideal synthesis is considered as one in which a target molecule is produced quantitatively in one step, from available and inexpensive raw materials, under environmentally harmless processes[39].

In continuation of above and our studies on the application of inorganic solid acid40, we found that anhydrous sodium metavanadate reacts with chlorosulfonic acid (1:1 mole ratio) to give vanadatesulfuric acid nanorod particles (VSA NRs). The reaction is performed easy, clean and without any workup (Scheme 1).

EXPERIMENTAL

Chemicals were purchased from Merck, Fluka and Aldrich chemical companies. X-ray diffraction analysis was carried out using a D8 ADVANCE, Bruker X-ray diffractometer using Cu-Kα radiation (λ = 1.5406 Å). Transmission electron microscopy was studied using a Philips, CM-10 TEM instrument operated at 100 kV. Melting points were determined using a Barnstead Electrothermal (BI 9300) apparatus and are uncorrected. IR spectra were obtained using a FT-IR JASCO-680 spectrometer instrument. NMR spectra were taken with a Bruker 400 MHz Ultrashield spectrometer at 400MHz (^{1}H) and 125 MHz (^{13}C) using $CDCl_3$ or DMSO-d_6 as the solvent with TMS as the internal standard.

Preparation of vanadatesulfuric acid

Anhydrous sodium metavanadate was prepared by drying of sodium metavanadate. monohydrate ($NaVO_3$. H_2O, MW = 139.94) in the oven at 250 °C for 4 hours. To 0.1 mol of chlorosulfonic acid (11.6 g, 7.7 mL) in 250 mL round bottom flask in the ice-bath, 0.1 mol (12.2 g) anhydrous sodium metavanadate was added gradually with stirring. After the completion of addition of anhydrous sodium metavanadate, the reaction mixture was shaken for 1 h. Then 50 mL of cold water was added to the reaction mixture and stirred for 10 minutes. The mixture was filtered and a dark red solid of vanadatesulfuric acid, 16.3 g (91%), Mp 256 °C (dec.) was obtained. Characteristic IR bands (KBr, cm^{-1}): 3540-3300 (OH, bs), 1640 (OH, m), 1250-1140 (S=O, bs), 1050 (S-O, m), 960 (V=O, m), 840 (V=O, m), 630 (V-O, m).

General procedure for the preparation of polyhydroquinolines

In a round-bottomed flask the aldehyde (1mmol), 1,3-cyclohexanedione derivatives (1 mmol), ammonium acetate (1.5 mmol), β-ketoester

(1 mmol) and VSA (10 mol%) were mixed thoroughly**.** The flask was heated at 80 °C with concomitant stirring. After completion of the reaction confirmed by TLC (eluent: EtOAc:*n*-hexane, 1:4), hot ethanol (10 mL) was added and filtered and separated solid catalyst. The solvent was evaporated and the crude products were recrystallized from ethanol, gave the pure products in 80-95% yields based on the starting aldehyde (Table 2). The products were characterized by IR, ^{1}H NMR, ^{13}C NMR and *via* comparison of their melting points with the reported ones. Spectroscopic data of new compounds:

2,7,7-Trimethyl-5-oxo-4-(4-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid methyl ester (Table 2, entry 23)

Mp: 251-253 °C; R_f = 0.53 (*n*-hexane:ethyl acetate = 4:1) ; IR (KBr): 3275, 3189, 3073, 2968, 1709, 1606, 1516, 1430, 1376, 1216, 1074, 864, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (s, 3H), 1.11 (s, 3H), 2.21-2.38 (m, 4H), 2.45 (s, 3H), 3.62 (s, 3H), 5.18 (s, 1H), 6.12 (brs, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 18.35, 18.52, 26.35, 28.99, 32.11, 36.38, 50.00, 50.78, 102.02, 109.00, 123.22, 128.55, 145.62, 146.40, 150.08, 154.78, 166.86, 194.25.

2,7,7-Trimethyl-5-oxo-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid methyl ester (Table 2, entry 24)

Mp: 259-261 °C; R_f = 0.55 (*n*-hexane:ethyl acetate = 4:1); IR (KBr): 3274, 3184, 3070, 2954, 1704, 1605, 1496, 1428, 1378, 1213, 1070, 846, 778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (s, 3H), 1.09 (s, 3H), 2.24-2.72 (m, 2H), 2.38 (s, 2H), 2.42 (s, 3H), 3.63 (s, 3H), 3.75 (s, 3H), 5.02 (s, 1H), 6.48 (brs, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 18.26, 18.53, 26.42, 29.12, 32.10, 34.66, 50.61, 54.80, 103.47, 110.19, 113.13, 128.18, 139.80, 144.95, 149.19, 157.24, 167.37, 194.29.

2,7,7-Trimethyl-5-oxo-4-(3-nitrophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid methyl ester (Table 2, entry 25)

Mp: 234-236 °C; R_f = 0.53 (*n*-hexane:ethyl acetate = 4:1) ; IR (KBr): 3298, 3077, 2975, 1709, 1700, 1606, 1482, 1427, 1377, 1221, 1073, 874, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (s, 3H), 1.11 (s, 3H), 2.18-2.45 (m, 4H), 2.44 (s, 3H), 3.64 (s, 3H), 5.18 (s, 1H), 6.3 (brs, 1H), 7.38-7.42 (t, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.99-8.01 (d, *J* = 6.0 Hz, 1H), 8.01 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 18.38, 18.52, 26.23 , 29.04, 32.17, 36.10, 49.97, 50.82 , 102.24, 109.19, 120.96, 121.68, 129.46, 134.14, 146.36, 147.49, 149.48, 150.11,166.90, 194.35.

2,7,7-Trimethyl-5-oxo-4-(4-bromophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid methyl ester (Table 2, entry 26)

Mp: 263-264 °C; R_f = 0.46 (*n*-hexane:ethyl acetate = 4:1) ; IR (KBr): 3288, 3198, 3076, 2957, 1682, 1605, 1491, 1379, 1225, 1073, 837, 774, 537 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.86 (s, 3H), 1.01 (s, 3H), 2.13-2.21 (m, 4H), 2.33 (s, 3H), 3.54 (s, 3H), 4.95 (s, 1H), 6.22 (brs, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 18.30, 18.53, 26.37, 29.05, 32.11, 50.10, 50.71, 102.64, 109.57, 118.73, 129.55, 130.41, 145.70, 146.78, 149.61, 167.10, 194.28.

2-Propyl-7,7-dimethyl-5-oxo-4-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (Table 2, entry 27)

Mp: 191-193 °C; R_f = 0.59 (*n*-hexane:ethyl acetate = 4:1) ; IR (KBr): 3278, 3213, 3086, 2959, 1698, 1606, 1490, 1380, 1211,1084, 851, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.68 (q, *J* = 6.5 Hz, 2H), 2.16-2.38 (m, 4H), 2.68-2.82 (m, 2H), 3.75 (s, 3H), 4.07(q, *J* = 7.2 Hz, 2H), 5.02 (s, 1H), 6.3 (brs, 1H), 6.74 (d, *J* = 4.8 Hz), 7.12 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 13.71 , 14.08 , 21.87, 26.39, 29.15, 31.90, 32.83, 34.87, 50.21, 54.77, 59.00, 103.64, 109.97, 113.02, 128.29, 139.99, 148.76, 149.41, 157.22, 166.61, 194.17.

2-Propyl-7,7-dimethyl-5-oxo-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (Table 2, entry 28)

Mp: 219-221 °C; R_f = 0.54 (*n*-hexane:ethyl acetate = 4:1); IR (KBr): 3275, 3210, 3086, 2961, 1703, 1609, 1489, 1380, 1211, 1084, 843, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (s, 3H), 1.05 (t, *J* = 7.2Hz, 3H), 1.19 (s, 3H), 1.21 (t, *J* =

7.2 Hz, 3H), 1.68 (m, 2H), 2.21 (d, *J* = 16.4 Hz, 2H), 2.29 (d, *J* = 16.2 Hz, 2H), 2.40 (d, *J* = 15.6 Hz, 2H), 2.69-2.84 (m, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 5.05 (s, 1H), 6.32 (brs, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm): 13.72, 14.04, 18.53, 21.87, 26.33, 29.10, 32.10, 32.83, 35.53, 50.09, 59.13, 102.87, 109.40, 127.68, 129.03, 130.16, 146.56, 149.51, 149.82, 166.33, 194.17.

RESULTS AND DISCUSSION

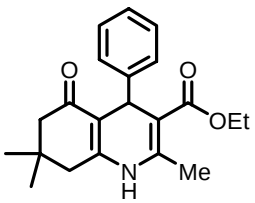
In this paper, we wish to report a novel, mild, cost-effective, and environmentally benign procedure for the one-pot synthesis of polyhydroquinoline derivatives by the condensation of aldehydes (aromatic, aliphatic, unsaturated, and heterocyclic), 5,5-dimethyl-1,3-cyclohexanedione (dimedone) or 1,3-cyclohexanedione, β-ketoesters and ammonium acetate in the presence of a catalytic amount of nanorod vanadatesulfuric acid (VSA) under solvent-free conditions (Scheme 2).

Characterization of vanadatesulfuric acid

Figure 1 exhibits the IR spectra of sodium metavanadate as substrate and Vanadatesulfuric acid. The infrared vibration bands found for $NaVO_3$ are assigned as follows (Fig 1(a)): In these spectra, several absorptions appear which are apparently the result of V-O stretching modes for each of several, different oxygen atoms according to the particular location or arrangement within the lattice[41]. At lower frequency, a broad and general absorption occurs which is apparently caused by lower frequency VO bonding. Here, the V-O stretching mode is observed as a medium band located at 950 cm^{-1}. These two spectra tend to locate the "normal" position for this stretching vibration between oxygen and vanadium. Other broad bands are present in the spectrum of sodium metavanadate, centering at 845 and 690 cm^{-1}. The VO_3^- structure consists of VO bondings of variable bond lengths, some of which vibrate at lower frequencies than others. The 950 cm^{-1} band has been assigned to a VO bond which is considerably shorter than other bonds in the structure; the 845 cm^{-1} band very probably arises from the stretching modes of the longer VO bonds. For Vanadatesulfuric acid, the infrared vibration bands are consigned as follows (Fig. 1(b)): The bands found at 3450 and 1640 cm^{-1} are attributed to the stretching and bending vibration of -OH group, respectively. The bands at 1050, and 1180 cm^{-1} are assigned for the sulfonic acid bonds, S–OH, S=O stretching, and S=O asymmetric stretching, respectively. The bands appearance in 960, 840 and 603 cm^{-1} related to V=O and V-O stretching.

Figure 2 depicts the X-ray diffraction (XRD) pattern of VSA. A number of prominent Bragg reflections reveal that the resultant particles of Vanadatesulfuric acid have a monoclinic structure (Space group: P2/m; a = 12.170 A°, b = 3.602 A°, c = 7.780 A°, JCPDS card no. 16-0601). The size of the VSA particles was also determined from X-ray

Table 1: Solvent effect on the model reaction catalyzed by VSA

Product	Solvent	Time(h)	Yield(%)
	CH_3CH_2OH	4	73
	CH_3OH	5	65
	H_2O	7	58
	CH_3CN	6	52
	$CHCl_3$	7	60
	Solvent-free	10 min	95

line broadening using the Debye-Scherrer formula ($D = 0.9\lambda/\beta\cos\theta$, where D is the average crystalline size, λ is the X-ray wavelength used, β is the angular line width at half maximum intensity, and β is the Bragg's angle). For the (001) reflection the average size of the VSA particles was estimated to be around 16 nm. The morphology and size of VSA were investigated by transmission electron microscopy (TEM) (Fig. 3). They had needle-like morphology with a narrow size distribution from 15 to 20 nm and a mean size of 17 nm, confirming the results calculated from Scherrer's equation. The presence of some larger particles should be attributed to aggregating or overlapping of smaller particles. In addition, elemental analysis of catalyst was performed by means of X-ray fluorescence analysis (XRF) that the obtain result confirmed the elemental composition of VSA.

Effect of solvent and catalyst concentration on the synthesis of polyhydroquinolines

In order to get the best experimental conditions, we initially studied the effect of various solvents and catalytic efficiency of VSA for the

Table 2: Synthesis of polyhydroquinoline derivatives in presence of VSA as catalyst[a]

Entry	R^1	R^2	R^3	R^4	Time (min)	Yields[b] (%)	Mp(°C) Found	Mp(°C) Reported
1	C_6H_5	H	OEt	Me	12	90	241-242	240-241
2	4-$NO_2C_6H_4$	H	OEt	Me	14	86	205-206	204-205
3	4-$CH_3C_6H_4$	H	OEt	Me	35	81	240-242	241-243
4	4-OHC_6H_4	H	OEt	Me	16	80	234-236	234-235
5	4-ClC_6H_4	H	OEt	Me	15	90	235-237	234-235
6	4-BrC_6H_4	H	OEt	Me	30	89	253-254	253-255
7	3-$NO_2C_6H_4$	H	OEt	Me	15	92	201-203	200-201
8	2-$NO_2C_6H_4$	H	OEt	Me	24	90	191-193	191-192
9	C_6H_5	Me	OEt	Me	10	95	202-204	203-204
10	4-$NO_2C_6H_4$	Me	OEt	Me	13	92	205-206	204-205
11	2-$NO_2C_6H_4$	Me	OEt	Me	21	90	205-207	206-207
12	2-$OCH_3C_6H_4$	Me	OEt	Me	12	85	193-195	193-195
13	3-BrC_6H_4	Me	OEt	Me	15	88	233-235	234-236
14	4-$CH_3C_6H_4$	Me	OEt	Me	25	87	260-262	261-263
15	4-BrC_6H_4	Me	OEt	Me	10	91	252-254	253-255
16	3-$NO_2C_6H_4$	Me	OEt	Me	10	93	179-181	178-180
17	2,4-$Cl_2C_6H_3$	Me	OEt	Me	25	92	242-244	240-243
18	$CH_3CH_2CH_2$	Me	OEt	Me	45	78	147-149	147-148
19	2-Furyl	Me	OEt	Me	10	80	247-248	246-248
20	C_6H_5–CH=CH	Me	OEt	Me	20	85	204-206	205-207
21	4-$CH_3C_6H_4$	Me	OMe	Me	20	85	274-276	>270
22	4-ClC_6H_4	Me	OMe	Me	5	91	219-221	220-222
23	4-$NO_2C_6H_4$	Me	OMe	Me	10	92	251-253	-
24	4-$CH_3OC_6H_4$	Me	OMe	Me	35	82	259-261	-
25	3-$NO_2C_6H_4$	Me	OMe	Me	30	87	234-236	-
26	4-BrC_6H_4	Me	OMe	Me	25	89	263-264	-
27	4-$CH_3OC_6H_4$	Me	OEt	Pr	35	85	191-193	-
28	4-ClC_6H_4	Me	OEt	Pr	20	89	219-221	-

[a]All products were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and comparison with these reported in the literature[27,29,33,42].

[b] Isolated yields.

Table 3: Reusability of vanadatesulfuric acid in the synthesis of 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester

Cycles	Isolated yield [a] (%)
Fresh	95
1	92
2	90
3	87
4	85

[a]Catalyst could be recycled by washing with ethanol and dried at 100 °C for 2h

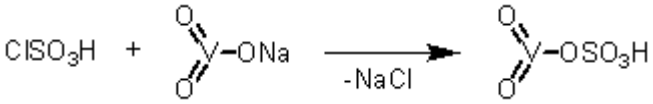
synthesis of 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester (Table 2, entry 9) using the model reaction of benzaldehyde (1mmol), dimedone (1 mmol), ethyl acetoacetate (1mmol), and ammonium acetate (1.5 mmol). As shown in Table 1, among the tested solvents, such as ethanol, methanol, water, acetonitrile and a solvent-free system, the best result was obtained after 10 min under solvent-free conditions in excellent yield (95%).

Figure 4 illustrates the effect of catalyst molar ratio on the conversion time of benzaldehyde as typical substrate under solvent-free conditions. It is important to note that no polyhydroquinoline derivatives were afforded when the reactions were

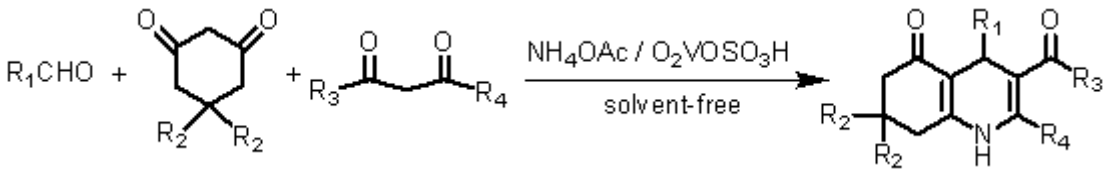
Table 4: Comparison of efficiency of various catalysts in the model reaction

Entry	Catalyst	conditions	Time(h)	Yield[a]	Ref
1	ceric ammonium nitrate	Solvent-free/rt	1	92	27
2	$Yb(OTf)_3$	Ethanol/rt	5	90	29
3	baker's yeast	phosphate buffer/rt	24	79	32
4	*p*-TSA	MeOH /reflux	2.5	90	31
5	$Hf(NPf_2)_4$	Solvent free/60 ^{0}C	3	95	43
6	$H_3PW_{12}O_{40}$	Solvent-free/80 ^{0}C	2	90	44
7	GuHCl	Solvent-free/rt	3	98	45
8	this work	Solvent-free/80 ^{0}C	10 min	95	-

[a] Isolated yields



Scheme 1



Scheme 2

performed in the absence of VSA in the reaction mixture. With increasing the catalyst, the reaction time is decreased up to 10% of catalyst molar ratio that was found to be an optimum amount in current conditions. The higher amount of catalyst was found that have not a notable effect on the reaction time and yield.

Therefore, this reaction was developed with other aldehydes, and the results are summarized in Table 2. The time of reaction was within 5-45 min, and high yields of polyhydroquinolines were obtained.

By using this heterogeneous catalyst, the aromatic aldehydes, bearing electron-donating substituents such as methyl, methoxy, and hydroxy and electron-withdrawing groups such as nitro and halid, gave high yields. The procedure worked well for vinyl as well as heterocyclic aldehydes in addition to aromatic aldehydes (Table 2). Acid-sensitive substrates such as cinnamaldehyde proceeded well to give the corresponding polyhydroquinoline without any side products (Entry 20). The results indicate the generality of the procedure, because aliphatic, aromatic, heterocyclic and α,β-unsaturated aldehydes were converted into the corresponding products in good to excellent yields in short reaction time as compared with some reported methods (Table 4).

To use of VSA in large scale synthesis

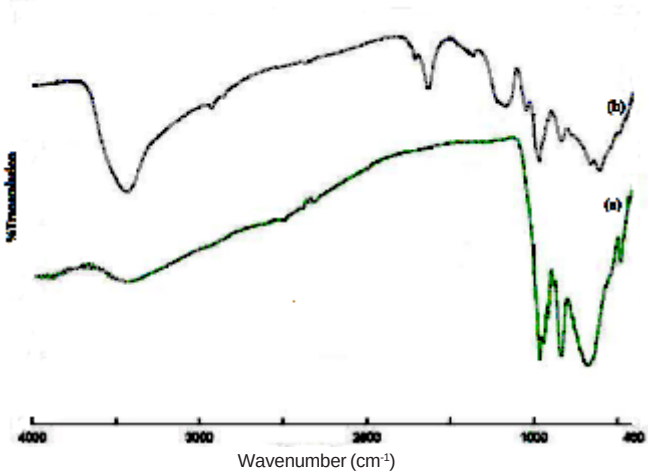


Fig. 1: FT-IR spectra of (a) sodium metavanadate; (b) vanadatesulfuric acid.

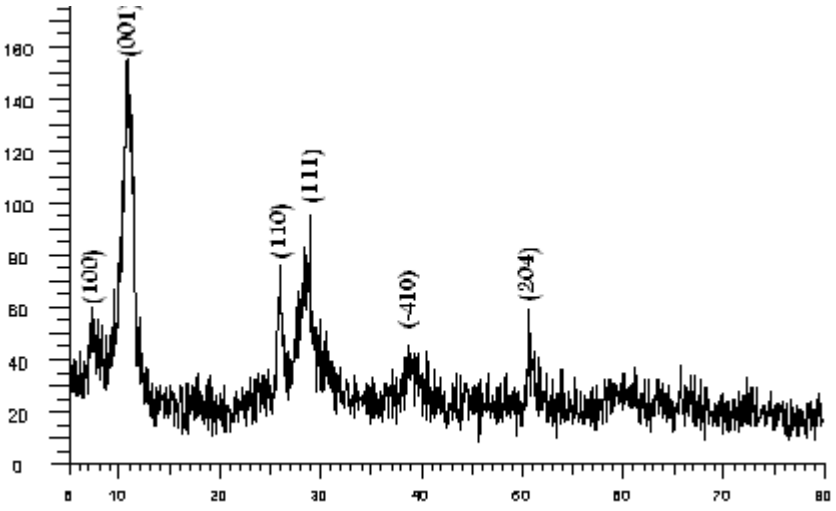
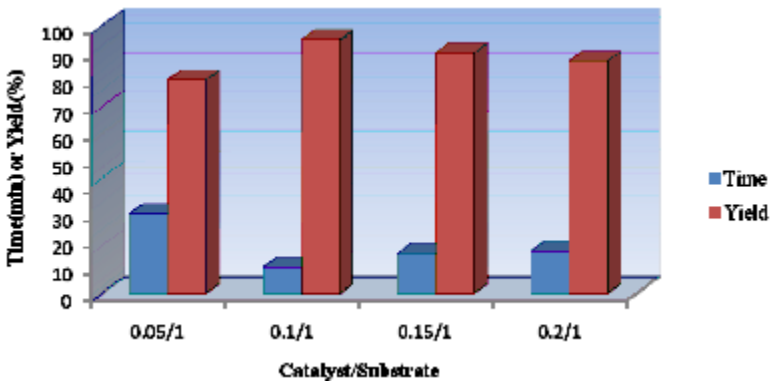


Fig. 2: Powder X-ray diffraction pattern of the VSA particles

Fig. 3: The TEM image showing needle-like VSA particles of 15-20 nm in size

especially in chemical laboratory, a typical reaction was performed for synthesis of 9 with tenfold amounts of reactants and catalyst with respect to one mentioned in the experimental section. The results showed the yield of 92% in these conditions that is comparable with one in table 2.

The reusability of the catalysts is an important benefit and makes them useful for commercial applications. Thus, the recovery and reusability of Vanadatesulfuric acid were investigated. The recyclability of the catalyst in the model reaction was checked. To achieve the reaction efficiency of recovered catalyst, the reaction mixture of **9** was filtered and washed with ethanol twice to give vanadatesulfuric acid. The recovered acid was dried and used again for synthesis of **9** that led to the yield of 90%. It can also be recovered and reused at least four times without any considerable loss of its activity (Table 3).



[a] Based on disappearance of benzaldehyde. For 0/1 catalyst to substrate after 10 h the conversion was 0%

Fig. 4: The catalyst amount effect on the synthesis of polyhydroquinolines[a]

Comparative results

In order to show the ability of our method with respect to previous reports, some of our results in comparison to some other methods are summarized in table 4. As shown, the yield/time ratio of the present method is better or comparable with the other reported results.

CONCLUSION

In summary, a novel and highly efficient method for the synthesis of polyhydroquinolines has been achieved by the multi-component condensation reaction of aldehydes (aromatic, aliphatic, unsaturated, and heterocyclic), 1,3-cyclohexanedione derivatives, ammonium acetate and β-ketoester using catalytic amount of the reusable and environmentally benign nonorod vanadatesulfuric acid (VSA) as a new solid acid catalyst under solvent-free conditions. The attractive features of this protocol are simple procedure, short reaction times, high yields, simple workup, reusability of the catalyst and simple purification of the products. Furthermore, this method is also

expected to find application in organic synthesis due to the low cost of the catalyst. This approach could make a valuable contribution to the existing processes in the field of polyhydroquinolines synthesis.

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