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Nanorod Vanadatesulfuric Acid as a Novel, Recyclable and Heterogeneous Catalyst for the One-Pot Synthesis of Tetrahydrobenzopyrans

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Vanadatesulfuric acid (VSA), as a novel and heterogeneous nanorod catalyst, was used for an efficient synthesis of tetrahydrobenzo[*b*]pyrans using an aldehydes, 1,3-cyclohexanediones or β-ketoester and malononitrile in C_2H_5OH/H_2O mixture under reflux conditions. VSA is prepared via the reaction of sodium metavanadate and chlorosulfonic acid in high purity. The catalyst was characterized by FT-IR, XRD, TEM and EDAX analysis. Compared to the conventional method, this method consistently has the advantage of high yields, simple workup, short reaction times and reusability of the catalyst.

Keywords: Vanadatesulfuric Acid, Tetrahydrobenzopyrans, Reusable Catalyst, Solvent-Free, Heterogeneous Catalyst, Nanorod Particle.

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1. INTRODUCTION

The compounds containing benzopyran rings which have received considerable attention in recent years due to their wide range of biological properties,[1] such as spasmolytic, diuretic, anti-coagulant, anti-cancer, anti-ancaphylactia activity.[2] In addition, they can be used in various applications as cognitive enhancers, for the treatment of neurodegenerative disease, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's diseases, Parkinson's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus.[3] 4*H*-Pyrans also constitute the structural unit of a series of natural products.[4] A number of 2-amino-4*H*-pyrans can be employed as photoactive materials,[5] pigments[6] potential biodegradable agrochemicals.[7]

The condensation of aromatic aldehydes with dimedone and malononitrile under reflux in acetic acid is a conventional method for synthesis of tetrahydro-4*H*-benzopyrans.[8] The wide biological and pharmaceutical activities of 4*H*-pyrans has led many researchers to synthesize them using various catalysts like tetramethylguanidinium trifluoroacetate as an ionic liquid,[9] diammonium hydrogen phosphate,[10] iodine,[11] *N*-methylimidazole,[12] sodium selenate,[13] and hexadecyldimethylbenzyl ammonium bromide.[14] Electrochemical reactions have also been used[15] as well as microwave heating in the solid state[16] and organic solvents or water.[8–12] Each of the above methods has its own merits, while some are plagued by limitations of poor yields, long reaction times, difficult workup procedures, effluent pollution, and the use of expensive catalysts that are harmful to the environment. Therefore, there is scope to develop alternative methods for the synthesis of tetrahydrobenzo[*b*]pyran derivatives under environmentally benign conditions.

In recent years, application of nanoparticles as catalyst have attracted worldwide attention due to high catalytic activity and improved selectivity.[17] In the context of green chemistry, the multicomponent reactions (MCRs) are very powerful and efficient bond forming tools in organic, combinatorial and medicinal chemistry.[18] The MCRs are very flexible, atom economic in nature, and proceed through a sequence of reaction equilibria, yielding the target product. Along with other reaction parameters, the nature of the catalyst plays a significant role in determining yield, selectivity, and general applicability. Thus, development of an inexpensive, mild, reusable, and general catalyst for MCRs remains an issue of interest.

From an environment protection laws point of view, there has been an increased emphasis on the design and use of environmentally benign solid acid or base heterogeneous catalysts to reduce the amount of toxic waste and byproducts from chemical processes.[19] The main advantage of a heterogeneous catalyst is that, being a solid material, it is easy to separate from the gas or liquid phase reactants and products after the catalytic reaction.

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Scheme 1. Synthesis of nanorod vanadatesulfuric acid.

Solid acids have emerged as potential alternate catalysts to the common liquid acids due to their safe nature, enhanced selectivity, requirements in catalytic amounts and easier work up.[20] The ease of separation without resulting into problem of waste disposal and option of reuse of the solid acid catalysts render the processes employing solid acid catalysts as green processes.

In continuation of the above and of our studies on the application of solid acids,[21] we found that anhydrous sodium metavanadate reacts with chlorosulfonic acid (1:1 mole ratio) in dry $CHCl_3$ to give nanorod vanadatesulfuric acid (VSA) particles. The reaction is performed easy, clean and the product, VSA, was isolated by simple filtration (Scheme 1).

2. RESULTS AND DISCUSSION

In connection with our recent interest in the application of solid acids,[21] herein we wish to report a simple and efficient method for synthesis of tetrahydrobenzo[*b*]pyran derivatives using the nanorod particles of vanadatesulfuric acid (VSA) as a new, green, recyclable and heterogeneous catalyst (Scheme 2).

2.1. Characterization of Vanadatesulfuric Acid

In the IR spectrum of $NaVO_3$, 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.[22] For vanadatesulfuric acid, the infrared vibration bands

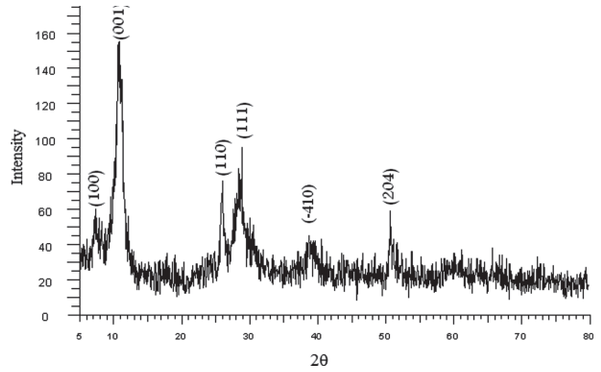


Fig. 1. Powder X-ray diffraction pattern of the VSA particles.

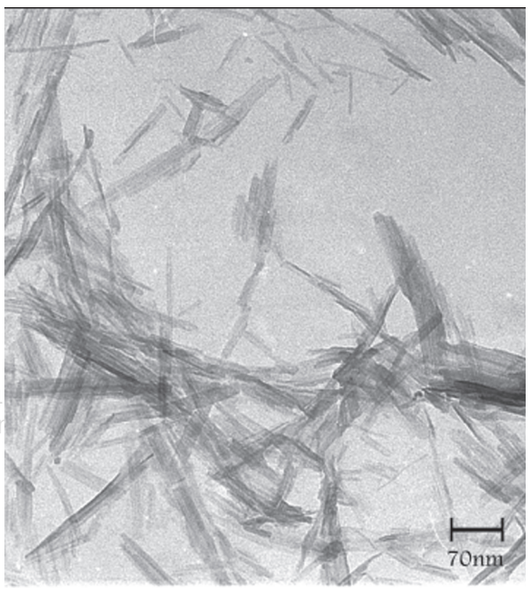
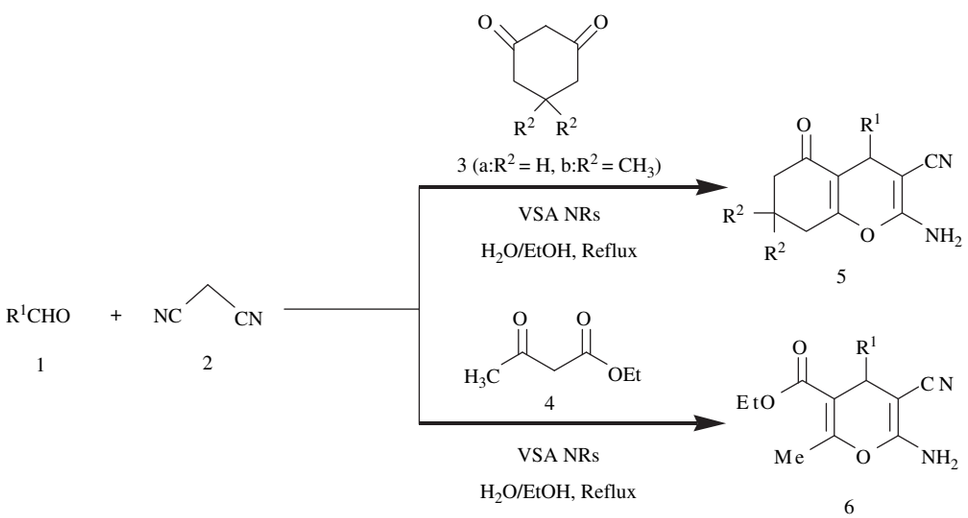


Fig. 2. The TEM image showing needle-like VSA particles of 15–20 nm in size.



Scheme 2. Nanorod VSA-catalyzed tetrahydrobenzo[b]pyrans formation reaction.

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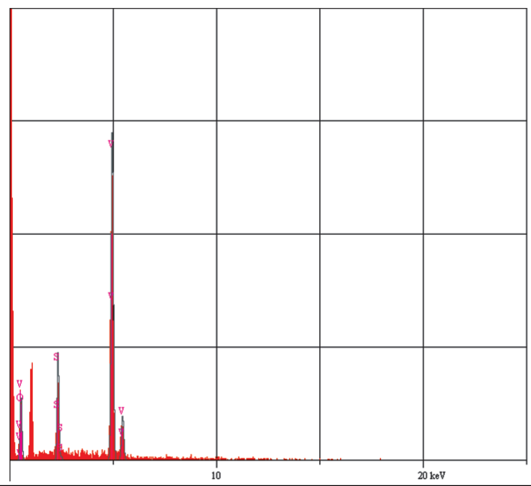

Elt.	Line	Intensity (c/s)	Atomic %	Conc	Units	
O	Ka	7.06	67.06	40.94	wt.%	
S	Ka	19.07	6.90	8.44	wt.%	
V	Ka	72.97	26.05	50.62	wt.%	
			100.00	100.00	wt.%	Total

Fig. 3. Energy dispersive spectroscopy (EDS) pattern of nanorod particles.

are consigned as follows: 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 1 shows the XRD patterns of vanadatesulfuric acid. A number of prominent Bragg reflections reveal that the resultant particles of vanadatesulfuric acid have a monoclinic structure (Space group: P2/m; $a = 12.170$ Å, $b = 3.602$ Å, $c = 7.780$ Å, JCPDS card no. 16-0601). The size of the VSA particles was also determined from X-ray line broadening using the Debye-Scherrer formula ($D = k\lambda/\beta\cos\theta$, where D is the average crystalline size, k is Sherrer constant, λ is the X-ray wavelength used, β is the angular line width at half maximum intensity, and θ is the Bragg's angle). For the (001) reflection the average size of the VSA particles was estimated to be around 16 nm.

Table II. Solvent effect on the reaction of benzaldehyde, malononitrile and dimedone catalyzed by VSA NRs.

Entry	Solvent (reflux)	Time (h)	Yield[a] (%)
1	CH_3CH_2OH	2.5	68
2	CH_3OH	5	30
3	CH_3CN	6	35
4	H_2O	3.5	42
5	CH_3CH_2OH/H_2O	0.33	92
6	Solvent-free[b]	10	15

Notes: [a]Isolated yields; [b]At 80 °C.

The morphology and size of the VSA were investigated by transmission electron microscopy (TEM) (Fig. 2). 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.

Energy-dispersive X-ray spectroscopy (EDAX) results confirm the presence of V, O, and S in nanorod particles of vanadatesulfuric acid (Fig. 3). The elemental distribution mapping of the catalyst by EDAX shows a constant vanadium: oxygen: sulfur signal ratio of 50.62:40.94:8.44 wt% over different areas.

2.2. Effect of Solvent and Catalyst Concentration on the Synthesis of Tetrahydrobenzopyrans

Initially, in order to evaluate the catalytic activity of VSA NRs, the three-component reaction of benzaldehyde, 5,5-dimethyl-1,3-cyclohexanedione (dimedone, **3b**) and malononitrile (**2**) under reflux condition as a model reaction was investigated. The corresponding product was obtained in 92% yield during 20 min. This compound and some tetrahydrobenzopyran derivatives have been synthesized under various conditions by other researchers that some of them is presented in Table I that have comparable or higher yield/time ratios in compared to current conditions.

Then, the solvent effect in the condensation of benzaldehyde (1 mmol), malononitrile (**2**, 1 mmol) and dimedone (**3b**, 1 mmol) in the presence of vanadatesulfuric acid

Table I. Comparison of efficiency of various catalysts in synthesis of tetrahydrobenzo[*b*]pyrans.

Entry	Catalyst	Amount of catalyst[b]	Conditions	Yield/Time[a]	Reference
1	Na_2SeO_4	10	C_2H_5OH/H_2O (reflux)	80–98/1–3	[23]
2	TMAH	10	H_2O (r.t)	79–92/0.5–2	[24]
3	Electrolysis (10 mA)	–	Electrode platinum	89–96/4–5	[25]
4	Molecular idoine	10	DMSO (reflux)	85–92/3–4	[26]
5	HDHBAB	12	H_2O (reflux)	84–95/5.5–8	[14]
6	Mg/La mixed oxide	5	CH_3OH (reflux)	52–92/1–3	[27]
7	TBAF	25	H_2O (reflux)	73–98/0.5–5	[28]
8	Baker's yeast	–	DMAc (r.t)	48–83/30	[29]
9	VSA	5	C_2H_5OH/H_2O (reflux)	76–95/0.08–0.8	–

Notes: [a]Values refer to yield (%)/time (h); [b]Amount of catalysts are in mol%.

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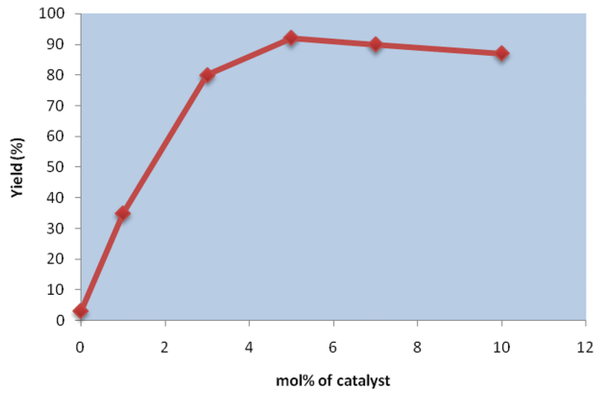

Fig. 4. Graph of isolated yield of 2-amino-4-phenyl-3-cyno-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran versus mol% of the catalyst (reaction conditions: benzaldehyde (1 mmol), malononitrile (**2**, 1 mmol) and dimedone (**3b**, 1 mmol), and time 20 min under refluxing EtOH/H_2O mixture).

NRs (0.05 mmol) as a model has been studied. As shown in Table II, among the tested solvents, such as ethanol, methanol, acetonitrile, water, chloroform and a solvent-free system, the best result was obtained after 20 min under refluxing C_2H_5OH/H_2O mixture conditions in excellent yield (92%).

The reaction conditions were then optimized by conducting the reaction in different catalyst loading. The best result was obtained by carrying out the reaction with 5 mol% of catalyst under reflux condition (Fig. 4).

In the absence of VSA, the model reaction gives, according to TLC monitoring, only trace of the product after 12 h under reflux condition. The conversion and yield of the corresponding tetrahydrobenzopyran increased with incremental increasing catalyst concentration from 1 to 5 mol%. Further addition of catalyst had no noticeable effect on the yield. This was because beyond a certain

Table III. Preparation of substituted tetrahydrobenzopyrans catalyzed by VSA.

Compounds	R^1	R^2	Time (min)	Yield[b] (%)	Mp (°C) Found[a]	Mp (°C) Reported
5a	C_6H_5	H	25	90	220–200	220–222[31]
5b	4-$O_2NC_6H_4$	H	15	91	224–226	225–227[32]
5c	4-$CH_3C_6H_4$	H	40	85	230–232	232–233[32]
5d	4-OHC_6H_4	H	30	82	235–236	234–236[33]
5e	4-ClC_6H_4	H	20	93	224–226	225–227[32]
5f	4-$CH_3OC_6H_4$	H	30	80	186–188	186–189[31]
5g	2,4-$Cl_2C_6H_3$	H	30	87	224–226	–
5h	3-$O_2NC_6H_4$	H	15	91	208–210	210–211[30]
5i	2-$O_2NC_6H_4$	H	25	90	197–199	196–198[33]
5j	C_6H_5	Me	20	92	226–28	228–230[24]
5k	4-$O_2NC_6H_4$	Me	5	92	177–179	176–178[30]
5l	3-$NO_2C_6H_4$	Me	10	90	210–212	211–214[24]
5m	2-$O_2NC_6H_4$	Me	20	90	222–224	224–226[23]
5n	4-BrC_6H_4	Me	10	92	205–207	207–209[24]
5o	3-Br-C_6H_4	Me	15	90	227–229	228–230[30]
5p	2-BrC_6H_4	Me	35	88	151–153	150–152[23]
5q	4-$OCH_3C_6H_4$	Me	30	83	198-200	197–199[30]
5r	4-OHC_6H_4	Me	30	85	206–208	204–205[30]
5s	4-$CH_3C_6H_4$	Me	35	85	212–214	210–213[24]
5t	2,4-ClC_6H_3	Me	25	92	181–183	180–182[24]
5u	$CH_3CH_2CH_2CHO$	Me	50	78	192–194	292–293[30]
5v	2-Furyl	Me	45	80	229–231	228–233[31]
5w	2-thiophene	Me	40	85	221–223	220–222[32]
5x	4-ClC_6H_4	Me	10	91	210–211	212–214[30]
5y	2-ClC_6H_4	Me	20	90	210–212	208–210[30]
5z	2-$CH_3OC_6H_4$	Me	35	82	202–203	–
5a′	2-OH-3-$CH_3OC_6H_3$	Me	40	87	232–234	–
5b′	2,6-$Cl_2C_6H_3$	Me	35	85	249–250	–
5c′	2-Cl-6-FC_6H_3	Me	40	87	206–207	–
6a	C_6H_5	–	20	90	194–195	195–196[34]
6b	4-ClC_6H_4	–	10	95	171–173	172–174[34]
6c	4-$CH_3C_6H_4$	–	35	83	176–178	177–179[34]
6d	4-$CH_3OC_6H_4$	–	30	84	143–145	142–144[30]
6e	4-$O_2NC_6H_4$	–	12	92	181–183	180–183[34]
6f	3-$O_2NC_6H_4$	–	13	91	180–182	182–183[34]
6g	CH_3CH_2CHO	–	45	76	184–186	185–186[27]
6h	2-Cl-6-FC_6H_3	–	35	89	210–212	–
6i	2-BrC_6H_4	–	25	88	191–193	–

Notes: [a]All products were characterized by ^1H NMR and IR spectroscopy and comparison with these reported in the literature; [b]Isolated yields.

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 5 mol% of the catalyst were used because of satisfactory yield of the product (92%) in reasonably short time. In other to improve the yields, the reaction is performed using different quantities of reagents. The best results were obtained with a 1:1:1 ratio of benzaldehyde, malononitrile and dimedone, respectively.

To generalize this procedure, a series of tetrahydrobenzopyrans were synthesized with benzaldehyde derivatives and the results are shown in Table III. The reaction worked well with electron withdrawing (NO_2, Br, Cl) as well as electron donating (Me, OMe, OH) substituents giving various tetrahydrobenzopyrans in yield 80–95% yields. Moreover, acid sensitive aldehydes such as furyl (**5v**) and thienyl carbaldehyde (**5w**) furnished products in yield of 80% and 85%, respectively. In addition, the aliphatic aldehydes such as butanal afforded a 78% yield in 50 min.

A standard leaching experiment was conducted to prove that the reaction is heterogeneous. The reaction was preceded for 10 min in the presence of catalyst and then catalyst was removed by filtration. The reaction was allowed to proceed without catalyst. There was no change in yield even after 10 h under reflux, indicating that no homogeneous catalyst was involved. The activity of the recycled VSA was also examined according to the typical experiment condition. It is noteworthy that the catalyst was recovered simply by filtration without any acidic or basic workup even after its fourth use. Two types of experiments were performed. After completion of the reaction of benzaldehyde, malononitrile and dimedone, the catalyst was recovered from the reaction mixture and recovered catalyst was dried in oven at 120 °C for 2 h prior to use. The recovered catalyst was then added to fresh substrates under the same experimental conditions for four runs without a noticeable decrease in the product yield and its catalytic activity (Table IV).

It well-known that vanadium based catalyst systems, including Vanadium phosphorous oxides catalysts such as $(VO)_2P_2O_7$ are prone to structural changes when used in liquid-phase oxidations.[35] The XRD diffraction patterns of fresh and used VSA catalyst in the synthesis of tetrahydrobenzopyrans are presented in Figure 5. Both the fresh catalyst and that recovered after fourth use exhibited similar XRD patterns, indicating that the structural properties of the catalysts were not affected by the reaction medium.

Infrared spectra of fresh and used VSA catalyst also confirmed the fact that the structure and morphology of the catalyst remained the same after recycling (Fig. 6).

Table IV. Reusability of vanadatesulfuric acid in the synthesis of tetrahydrobenzopyran of benzaldehyde, malononitrile and dimedone.

	Isolated yield[a] (%)	
Cycles	Type 1[b]	Type 2[c]
Fresh	92	92
1	91	90
2	92	89
3	92	87
4	90	85

Notes: [a]Catalyst could be recycled by washing with ethanol and dried at 120 °C for 2 h; [b]With makeup, loss of catalyst (<4%) was made up by fresh catalyst; [c]Without makeup.

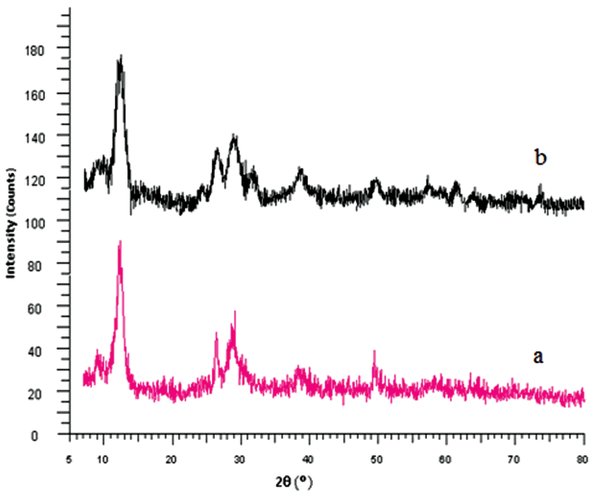

Fig. 5. XRD patterns of the catalyst (a) fresh catalyst (b) recovered catalyst after fourth use.

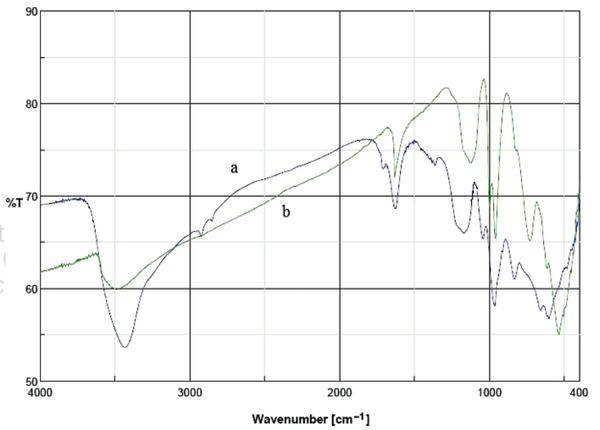

Fig. 6. FT-IR spectra of vanadatesulfuric acid: (a) before use and (b) after reuse four times.

3. CONCLUSION

We have found a rapid and very efficient, nanorod vanadatesulfuric acid (VSA NRs) catalyzed one-pot three-component reaction of β-dicarbonyl compounds, benzaldehyde derivatives and an active methylene compound for the synthesis of tetrahydrobenzo[*b*]pyran derivatives in aqueous ethanol media. This novel catalytic system demonstrates the advantages of environmentally benign

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character, mild reaction conditions, short reaction times, high yields, easy handling as well as good reusability. Moreover, non-hygroscopic and inexpensive for this transformation are other advantages of this procedure.

4. EXPERIMENTAL

Chemicals were purchased from Merck, Fluka and Aldrich chemical companies. Transmission electron microscopy was studied using a Philips, CM-10 TEM instrument operated at 100 kV. The compositional analysis is carried out using energy dispersive X-ray spectroscopy (EDAX). 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 400 MHz (^{1}H) and 125 MHz (^{13}C) using DMSO-d_6 as the solvent with TMS as the internal standard.

4.1. Preparation of Vanadatesulfuric Acid

Anhydrous sodium metavanadate was prepared by drying of sodium metavanadate monohydrate ($NaVO_3 \cdot H_2O$, MW = 139.94) in the oven at 200 °C for 4 h. To mixture of chlorosulfonic acid (0.1 mol, 11.6 g, 7.7 mL) and dry $CHCl_3$ in 250 mL round bottom flask in an ice-bath, anhydrous sodium metavanadate (0.1 mol, 12.2 g) was added gradually with vigorous stirring. After the completion of addition of anhydrous sodium metavanadate, the reaction 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).

4.2. General Procedure for Preparation of Tetrahydrobenzo[*b*]pyrans

A mixture of aldehyde (1 mmol), β-dicarbonyl (1 mmol) and malononitrile (1 mmol) and VSA (0.05 mmol) in EtOH/H_2O (10 mL) was heated under reflux condition with stirring for an appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate: *n*-hexane (1:4) as eluent. After completion of the reaction, the catalyst was separated by filtration and the filtrate was cooled and the solid was collected and washed with water and recrystallized from ethanol to give pure product in 75–95% yields (Table III). The physical and spectroscopic data of new compounds is given below:

2-amino-4-(2,4-dichlorophenyl)-3-cyano–5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]*pyran (Table* III, *5 g)*: Mp: 224–226 °C; $R_f = 0.51$ (*n*-hexane:ethyl acetate = 4:1); IR (KBr): 3314, 3158, 2962, 2189, 1682, 1649, 1608, 1469, 1420, 1368, 1213, 1049, 861, 765 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.87–1.99 (*m*, 2 H), 2.17–2.33 (*m*, 2 H), 2.57–2.66 (*m*, 2 H), 4.68 (*s*, 1 H), 7.07 (*s*, 2 H), 7.21 (*d*, $J = 8.4$ Hz, 1 H), 7.34 (*dd*, $J = 6.4$ Hz, $J = 2.0$ Hz, 1 H), 7.51 (*d*, $J = 1.6$ Hz, 1 H).; ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 19.73, 26.42, 32.35, 36.20, 56.28, 112.38, 119.13, 127.69, 128.56, 131.22, 131.68, 132.95, 140.88, 158.50, 165.34, 195.90; Anal. Calcd. for $C_{16}H_{12}Cl_2N_2O_2$: C, 57.33; H, 3.61; Cl, 21.15; N, 8.36; O, 9.55; found: C 57.40, H 3.70, N 8.30.

2-amino-4-(2-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]*pyran (Table* III, *5z)*: Mp: 202–203 °C; $R_f = 0.56$ (*n*-hexane:ethyl acetate = 4:1); IR (KBr): 3396, 3329, 3011, 2965, 2188, 1686, 1654, 1605, 1493, 1371, 1212, 1037, 858, 755 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.97 (*s*, 3 H), 1.05 (*s*, 3 H), 2.07 (*d*, $J = 16.0$ Hz, 1 H), 2.26 (*d*, $J = 16.0$ Hz, 1 H), 2.46 (*d*, $J = 17.2$ Hz, 1 H), 2.56 (*d*, $J = 17.2$ Hz, 1 H), 3.75 (*s*, 3 H), 4.49 (*s*, 1 H), 6.84 (*m*, 1 H), 6.86 (*s*, 2 H), 6.96 (*d*, $J = 8.4$ Hz, 1 H), 7.00 (*d*, $J = 6.8$ Hz, 1 H), 7.14–7.18 (*m*, 1 H).; ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 25.67, 26.50, 28.59, 30.29, 31.74, 50.00, 55.56, 57.29, 111.42, 111.84, 119.83, 120.29, 127.77, 128.52, 132.11, 156.78, 158.96, 163.07, 195.56.; Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64; O, 14.80; found: C 70.43, H 6.30, N 8.56.

2-amino-4-(2-hydroxy-3-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]*pyran (Table* III, *5a′)*: Mp: 232–234 °C; $R_f = 0.46$ (*n*-hexane:ethyl acetate = 4:1); IR (KBr): 3577, 3329, 3180, 3198, 3076, 2961, 2210, 1692, 1644, 1605, 1491, 1383, 1235, 1088, 845, 748 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.95 (*s*, 3 H), 1.09 (*s*, 3 H), 2.07 (*d*, $J = 16.0$ Hz, 1 H), 2.26 (*d*, $J = 16.0$ Hz, 1 H), 2.46 (*d*, $J = 17.2$ Hz, 1 H), 2.56 (*d*, $J = 17.2$ Hz, 1 H), 3.93 (*s*, 3 H), 4.65 (*s*, 1 H), 7.32 (*s*, 2 H), 7.35 (*d*, $J = 8.0$ Hz, 1 H), 7.40 (t, $J = 7.0$ Hz, 1 H), 7.50 (d, $J = 8.0$ Hz, 1 H), 10.95 (*s*, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6)δ (ppm): 26.04, 26.30, 28.95, 31.74, 32.07, 45.24, 49.65, 56.02, 116.84, 117.53, 120.89, 124.64, 125.06, 125.36, 143.85, 155.17, 164.66, 167.00, 196.30; Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23; O, 18.80; found: C 67.12, H 5.85, N 8.30.

2-amino-4-(2,6-dichlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]*pyran (Table* III, *5b′)*: Mp: 249–251 °C; $R_f = 0.53$ (*n*-hexane: ethyl acetate = 4:1); IR (KBr): 3417, 3330, 3035, 2960, 2190, 1685, 1655, 1603, 1455, 1419, 1362, 1218, 1032, 884, 783 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.99 (*s*, 3 H), 1.04 (*s*, 3 H), 2.06 (*d*, $J = 16.0$ Hz, 1 H), 2.26 (*d*, $J = 16.0$ Hz, 1 H), 2.37 (*d*, $J = 17.2$ Hz, 1 H), 2.53 (*d*, $J = 17.2$ Hz, 1 H), 5.21 (*s*, 1 H), 7.12 (*s*, 2 H), 7.24 (*t*, $J = 8.0$ Hz, 1 H), 7.35 (*dd*, $J = 7.2$ Hz, $J = 0.8$ Hz, 1 H), 7.46 (*dd*, $J = 6.8$ Hz, $J = 1.2$ Hz, 1 H).; ^{13}C NMR (125 MHz, DMSO-d_6)δ (ppm):26.84, 28.44, 31.51,

32.22, 49.89, 53.47, 55.99, 109.93, 118.96, 128.45, 128.95, 130.17, 134.11, 135.79, 136.30, 159.40, 163.73, 195.66.; Anal. Calcd. for $C_{18}H_{16}Cl_2N_2O_2$: C, 59.52; H, 4.44; Cl, 19.52; N, 7.71; O, 8.81; found: C 59.60, H 4.52, N 7.65.

2-amino-4-(2-chloro-6-fluorophenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (Table III*, 5c′)*: Mp: 206–207 °C; $R_f = 0.55$ (*n*-hexane:ethyl acetate = 4:1); IR (KBr): 3415, 3330, 3070, 2964, 2197, 1683, 1654, 1600, 1453, 1417, 1369, 1214, 1037, 898, 781 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.95 (s, 3 H), 1.05 (s, 3 H), 2.07 (d, $J = 16.0$ Hz, 1 H), 2.28 (d, $J = 16.4$ Hz, 1 H), 2.37 (d, $J = 17.2$ Hz, 1 H), 2.53 (d, $J = 17.2$ Hz, 1 H), 4.89 (s, 1 H), 7.13 (s, 2 H), 7.15–7.18 (m, 1 H), 7.26–7.29 (m, 2 H); ^{13}C NMR (125 MHz, DMSO$-d_6$) δ (ppm): 26.25, 28.59, 29.49, 31.66, 49.83, 51.87, 56.00, 112.11, 114.04, 119.21, 123.69, 129.06, 129.16, 132.76, 133.59, 159.29, 163.54, 195.66.; Anal. Calcd. for $C_{18}H_{16}ClFN_2O_2$: C, 62.34; H, 4.65; Cl, 10.22; F, 5.48; N, 8.08; O, 9.23; found: C 62.44, H 4.73, N 8.17.

5-Ethoxycarbonyl-2-amino-4-(2-chloro-6-fluorophenyl)-3-cyano-6-methyl-4H-pyran (Table III*, 6h)*: Mp: 210–212 °C; $R_f = 0.53$ (*n*-hexane:ethyl acetate = 4:1); IR (KBr): 3474, 3324, 3065, 2961, 2186, 1683, 1658, 1593, 1466, 1367, 1216, 1083, 890, 780, 544 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6)δ (ppm): 1.01 (t, $J = 7.2$ Hz, 3 H), 2.29 (s, 3 H), 3.95 (q, $J = 6.4$ Hz, 2 H), 5.03 (s, 1 H), 7.03 (s, 2 H), 7.17 (t, $J = 2.8$ Hz, 1 H), 7.31 (d, $J = 2.4$ Hz, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6)δ (ppm): 13.53, 18.15, 31.65, 53.10, 60.11, 103.48, 115.14, 119.18, 125.84, 128.53, 129.33, 133.61, 158.56, 159.10, 160.33, 165.10.; Anal. Calcd. for $C_{16}H_{14}ClFN_2O_3$: C, 57.07; H, 4.19; Cl, 10.53; F, 5.64; N, 8.32; O, 14.25; found: C 57.15, H 4.27, N 8.24.

5-Ethoxycarbonyl-2-amino-4-(2-bromophenyl)-3-cyano-6-methyl-4H-pyran (Table III*, 6i):* Mp: 191–193 °C; $R_f = 0.58$ (*n*-hexane:ethyl acetate = 4:1); IR (KBr): 3433, 3333, 3066, 2977, 2190, 1686, 1641, 1602, 1466, 1379, 1213, 1061, 827, 743 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.97 (t, $J = 7.2$ Hz, 3 H), 2.34 (s, 3 H), 3.92 (q, $J = 4.0$ Hz, 2H), 4.88 (s, 1 H), 6.95 (s, 2 H), 7.13–7.20 (m, 2 H), 7.33–7.37 (m, 1 H), 7.56 (dd, $J = 6.8$ Hz, $J = 1.2$ Hz, 1 H).; ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 13.62, 18.07, 37.51, 56.14, 60.06, 106.19, 119.05, 122.61, 128.36, 128.4, 132.46, 143.84, 157.73, 158.35, 165.12; Anal. Calcd. for $C_{16}H_{15}BrN_2O_3$: C, 52.91; H, 4.16; Br, 22.00; N, 7.71; O, 13.22; found: C 53.00, H 4.23, N 7.64.

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