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Ammonium metavanadate: an effective catalyst for synthesis of dihydropyrimidinones under solvent-free conditions

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ABSTRACT

Ammonium metavanadate (NH_4VO_3) is an inexpensive, efficient and mild catalyst for the three-component condensation reaction of aldehydes, β-ketoester and urea/thiourea. Thismethod offers several advantages including relatively short reaction times, solvent-free,easywork-up procedure and good to high yields of product © 2015 Trade Science Inc. - INDIA

KEYWORDS

Biginelli reaction;
Ammonium metavanadate;
Dihydropyrimidinones;
Solvent-free.

INTRODUCTION

Dihydropyrimidinones (DHPMs) and related compounds have been found to exhibit a wide spectrum of biological activities such as antiviral[1], antitumor[2] and antibacterial[3]. Appropriately functionalized dihydropyrimidinones have emerged as potent calcium channel blockers[4], antihypertensive agents[5] and α-1a adrenergic antagonists[6]. Moreover, several marine alkaloids containing the DHPMs core unit have shown interesting biological properties. In particular, batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors[7]. Thus, the synthesis of this heterocyclic compounds is of much current importance.

In order to improve the efficiency of the Biginelli reaction several Lewis catalysts such as $ZrCl_4$[8], $Cu(OTf)_2$[9], $Zn(OTf)_2$[10], chloroacetic acid[11] and ionic liquids such as $(EtNH_3)NO_2$[12], $LaCl_3.7H_2O$[13], In(III)-halides[14], $(bmim)PF_4$ or BF_4[15], cellulose sulfuric acid (CSA)[16], polymer-supported 4-aminoformoyldiphenylammonium triflate (PS-AFDPAT)[17], boric acid[18], $Fe(HSO_4$[19], 12-Molybdophosphoric acid[20], sulfonic acid on to silica[21], propane phosphonic acid anhydride[22], montmorilonite KSF[23], triphenylphosphine[24] have been reported. In most cases these reactions suffer from the long reaction time or exotic reaction conditions.

In recent years, solvent-free organic synthesis have offered more advantages as compared to their homogeneous counterparts due to the growing concern for the influence of organic solvent on the environment as well as on human body, economical demands and simplicity in the processes[25].

Hence the search continues for a better catalyst in the synthesis of in dihydropyrimidinones terms of operational simplicity and economic viability. Herein

we report the use of ammonium metavanadate (NH_4VO_3) as a water soluble, inorganic acid[26] that meets the demand for an economic catalyst. It is employed similar to vanadium pentoxide[27] as a catalyst in oxidation reactions with other co-catalysts[28]. It is a reagent used in analytical chemistry, the photographic industry, and the textile industry[29]. This is the first report of utilizing ammonium metavanadate as a catalyst for the synthesis of dihydropyrimidinones

EXPERIMENTAL

Apparatus and reagents

All the reagents and aromatic aldehydes were obtained from commercial suppliers and were not purified. Melting points were determined in open capillaries and are uncorrected. The completion of reactions was monitored by TLC. IR spectra were recorded on a matrix of KBr with Perkin-Elmer 1430 spectrometer. ^{1}H NMR spectra were recorded on Varian NMR spectrometer, Model Mercury Plus (400MHz), Mass spectra [ES-MS] were recorded on a Water-Micro mass Quattro-II spectrophotometer. Products of the following procedures were characterized by their physical constants, and compared with authentic samples by IR and NMR spectroscopy.

General procedure for the synthesis of dihydropyrimidinones (1-16)

A mixture of aldehyde (4 mmol), â-ketoester (4 mmol) urea or thiourea (6 mmol) and ammonium metavanadate (NH_4VO_3) (0.2 mmol) was heated in an oil bath (100°C) for 1-2 hrs After completion (monitored by TLC), the reaction was cooled to room temperature and the mixture was poured on crushed ice, upon which a solid material was separated and then filtered and recrystallized from ethanol to produce the desired product in 85-94% yields.

Spectral data of the the principal products

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (4a)

^{1}HNMR(DMSO-d_6) ä: 1.08 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.22 (s, 3H, CH_3), 3.67 (q, 2H, J = 7.1 Hz,OCH_2), 5.05 (d, 1H, -CH), 7.28-7.55 (m, 5H, Ar-H), 7.75 (s, 1H, NH), 9.20 (s, 1H, NH); IR (õmax.; KBr, cm-1): 3440, 3240, 1722, 1638;m/z = 261 (M+)

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4e)

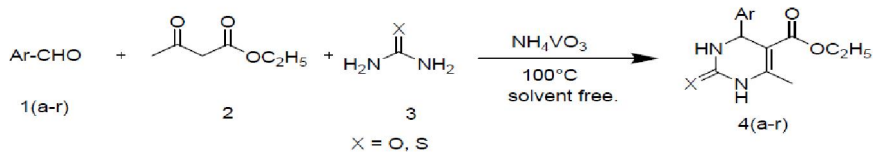
^{1}H NMR (DMSO-d_6) ä: 1.17(t,3H,OCH_2-CH_3,J = 7.2Hz) 4.12 (q, 2H J = 7.2Hz), 3.78(s, 3H, OCH_3), 2.34(s, 3H, CH_3), 5.35(s, 1H CH), 7.21(d, 2H,ArH J = 9.10Hz), 6.8(d, 2H, ArH J = 9.10Hz), 5.7(s, 1H, NH),), 8.15(s, 1H,NH). IR (õmax.KBr) 3240, 3114, 2956, 2821, 1701, 1647, 1419, 1367, 1220, 781cm-1. m/z = 291(M+)

5-(Ethoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one(4i)

^{1}H-NMR (DMSO-d_6) ä: 1.11 (t, 3H, J = 7.04 Hz,OCH_2CH_3), 2.32 (s, 3H, CH_3), 4.03. (q, 2H, J= 7.04Hz, OCH_2CH_3), 5.58 (d, 1H, J = 2.28, -CH), 7.51(d, 2H, J = 9.18, Ar-H), 7.69 (s, 1H, NH),8.16 (d, 2H, J = 9.18, Ar-H), 9.05 (s, 1H, NH); IR (õímax.;KBr, cm-1): 3235, 1740,1631;m/z = 306(M+)

RESULT AND DISCUSSION

In continuation of our research devoted to interest in the development of novel synthetic methodologies on Biginelli reaction[12, 29, 30]. Herein, we report a simple, efficient, and rapid method for the synthesis of dihydropyrimidinones catalyzed by ammonium metavanadate. Scheme 1.



Scheme 1

TABLE 1 : Screening of concentration of catalyst[a]

Entry	NH_4VO_3 (mmol)	Yield (%)[b]	Time(min)
1	0.05	76	85
2	0.10	80	75
3	0.15	85	70
4	0.20	94	65
5	0.25	94	65

[a]Reaction Conditions: 1a (4 mmol), 2 (4 mmol), 3 urea (6 mmole), solvent-free at 100°C. [b]Isolated yields

TABLE 2 : Screening of solvents[a]

Entry	Solvent	Time (min)	Yield (%)[b]
1	Tetrahydrofuran	65	15
2	Dichloromethane	65	20
3	Toluene	65	22
4	Dimethylforamide	65	25
5	Ethanol	65	30
6	Neat	65	94

[a]Reaction Conditions: 1a (4 mmol), 2 (4 mmol), 3 urea (6. mmol) NH_4VO_3, (0.2 mmol) and solvent free at 100°C. [b]Isolated yields.

TABLE 3 : Comparison with reported procedure

Entry	Method	Time (hrs.)/Yield(%)	
		C_6H_5	4-$OCH_3C_6H_4$
1	Present	1/94	1.2/92
2	$Fe(HSO_4)_3$ [19]	1.5/86	2/90
3	12-Molybdophosphoric acid[20]	5/80	4/70
4	Sulfonic acid[21]	18/90	7/92
5	Propane phosphonic acid anhydride[22]	6/77	6/59
6	Montmorilonite KSF[23]	48/82	48/79
7	PS-AFDPAT[17]	5/90	5/94
8	CSA[16]	2/96	3/93

To optimize the reaction conditions, the reaction of benzaldehyde, ethyl acetoacetate and urea was selected as model to investigate the effects of catalyst at different amount of ammonium metavanadate (NH_4VO_3) on yield and time TABLE 1.

To evaluate the effect of solvent, various solvents such as tetrahydrofuran dichloromethane, toluene, dimethylformamide, ethanol and solvent-free were used for the standard model reaction. Predictably, it was observed that the use of solvent retarded the reaction rate and afforded the desired product in much lower yields TABLE-2, entry 1-5.

The optimized conditions for the condensation of 4 mmol benzaldehyde, 4 mmol ethyl acetoacetate and 6 mmol urea or thiourea in the presence of 0.2 mmol ammonium metavanadate, solvent free conditions heat at 100°C on oil bath for 1-2 hr In a similar fashion, a variety of aromatic and heterocyclic aldehydes underwent three-component condensation smoothly to afford a wide range of substituted DHPMs TABLE 4. The reaction is most computable with various electrons donating or electron-withdrawing

Substituents such as -OH, -OCH_3, -F, -Cl, -NO_2 and heterocyclic aldehydes like furan under go the reaction. Thiourea has been used with similar success to produce the corresponding thio-derivatives of DHPMs.

In order to show the merit of this method, TABLE 3 compares some of our results with some of the before mentioned methods for the synthesis of 3,4-dihydropyrimidine-2(*1H*)-ones as show in TABLE 3.

TABLE 4 : Synthesis of 3,4-dihydropyrimidin-2(*1h*)-ones in the presence of ammonium metavanadate at 100°C

Entry	Ar	R	X	Time (min)[b]	Yield(%)[c]	M.p°C	
						Found	Reported
4a	C_6H_5	Et	O	65	94	200-202	202-204[18]
4b	2-$OCH_3C_6H_4$	Et	O	90	88	260-261	261-262[18]
4c	4-HOC_6H_4	Et	O	100	93	210-212	210-211[31]
4d	4-ClC_6H_4	Et	O	75	87	212-213	213-215[18]
4e	4-$OCH_3C_6H_4$	Et	O	80	92	199-201	201-203[18]
4f	3-ClC_6H_4	Et	O	85	89	192-194	193-195[19]
4g	4-FC_6H_4	Et	O	70	87	183-185	185-186[30]
4h	2-Furyl	Et	O	70	89	209-210	206-208[31]
4i	4-$NO_2C_6H_4$	Et	O	95	92	206-208	208-210[19]
4j	2-ClC_6H_4	Et	O	80	93	218-220	218-220[31]
4k	2-$NO_2C_6H_4$	Et	O	85	90	207-208	206-208[18]
4l	3-$NO_2C_6H_4$	Et	O	80	91	226-228.	227-229[18]
4m	3-$NO_2C_6H_4$	Et	S	85	90	204-206	206-207[18]
4n	C_6H_5	Et	S	75	92	208-210	209-211[18]
4o	4-ClC_6H_4	Et	S	85	89	192-194	192-195[09]
4p	C_6H_5	Me	O	70	90	230-232	231-233[19]
4q	4-ClC_6H_4	Me	O	75	85	206-208	205-206[19]
4r	C_6H_5	Me	S	85	89	228-230	228-229[19]

[a]Reaction Conditions: 1 (4mmol), 2 (4 mmol), 3 (6mmol), NH_4VO_3 (0.2mol), solvent-free at 100°C. [b]Time in min. [c]Isolated yields

CONCLUSION

Ammonium metavanadate (NH_4VO_3) is a readily available, inexpensive, and efficient catalyst for the synthesis of variety of dihydropyrimidinones derivatives. The remarkable advantages offered by this method are solvent-free reaction conditions, reactions, short reaction times, ease of product isolations, and high yields. We believe that this method is a useful addition to the present methodology for the synthesis of dihydropyrimidinones.

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