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Synthesis of Some Biginelli-type Products: Nano Alumina Sulfonic acid (NASA) Catalyzed under Solvent-free Condition

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Abstract

Biginelli-type reaction was developed by means of a three-component condensation of an aldehyde, ethyl acetoacetate, urea or thiourea and nano alumina sulfonic acid (Al_2O_3-SO_3H) (NASA) as catalyzed. It is carried out under different conditions. In all conditions, the desired products are obtained in high yields after relatively short reaction times. Nevertheless, the reactions proceeded faster and in higher yields when they were carried out under solvent-free at 120 °C. Improving product yields and reaction time, NASA was used in a catalytic amount (0.027 mol%). An amount of catalyst used in these reactions is far less than reported (15 mol%). The rate of the reaction was also 24 times faster than the previous rate reported by Shaterian and co-workers by the same yield. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) techniques are used to characterize the microstructural of NASA. Finally, the mechanism of this reaction was studied.

Keywords: *Nano Al_2O_3-SO_3H, Biginelli-type, Solvent-free, SEM, TEM.*

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Introduction

In many years, dihydropyrimidinones (DHPMs) and their derivatives have exhibited a fascinating variety in natural, synthetic heterocyclic compounds. Biginelli-type products were used in pharmacological, therapeutic and bioorganic chemistry mainly due to their wide range of biological activities [1–3]. In addition, these heterocyclic compounds are being studied as calcium channel blockers, antihypertensive agents, alpha-la-antagonists and neuropeptide Y(NPY) antagonists [4,5]. 3,4-dihydropyrimidinethiones (3,4-DHPMs) have been suggested to be useful building blocks for the synthesis of natural products, such as the batzelladine family of polycyclic marine alkaloids [6,7]. These new alkaloids have been found to be an effective HIV gp-120-CD4 inhibitors [8,9].

Therefore, in 1893 an Italian chemist Pietro Biginelli reported the most simple and straightforward procedure for the synthesis of DHPMs for the first time. This reaction involves a three-component one-pot condensation of benzaldehyde, ethyl acetoacetate and urea under strongly acidic conditions [10]. But, this reaction generally requires severe conditions, long reaction times and gives low yields. To overcome these drawbacks, several protocols for the synthesis of DHPMs have been developed to improve and modify this reaction [11-13]. This report describes a one-pot multicomponent process for the synthesis of Biginelli-type products using NASA as the heterogeneous catalysts under solvent-free conditions at 120 °C (Scheme 2). Furthermore, the characteristic of NASA was explained by means of the scanning electron microscopy (SEM) and transmission electron microscopy (TEM) techniques (Figure 1).

To show the merit of the present work in comparison with reported results in the literature, we compared results of NASA with different catalysts in the reaction of ethyl acetoacetate, urea or thiourea, and different aldehydes in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones.

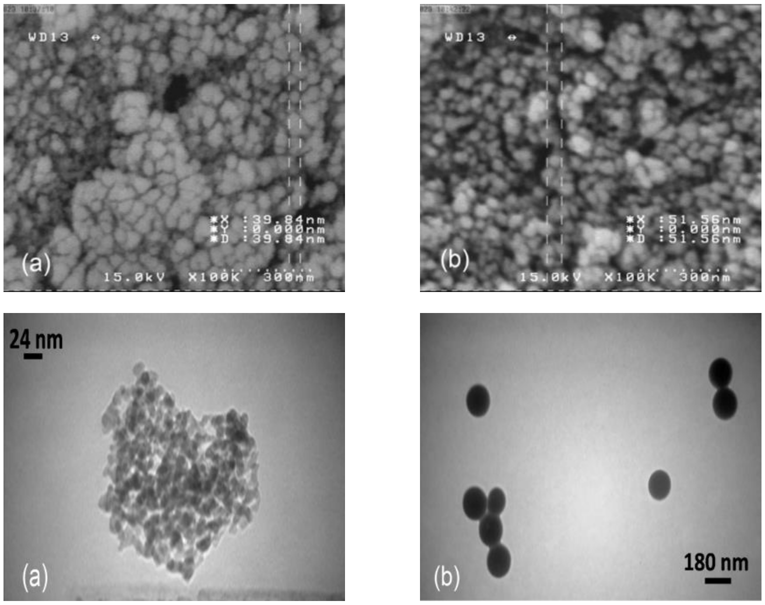


Figure 1. SEM and TEM images of (a) nano alumina and (b) NASA.

Experimental

Melting points were determined on an IA 9100 apparatus and are uncorrected. IR spectra were recorded from KBr discs on a Shimadzu apparatus IR 435. ^{1}H NMR spectra were recorded using a Bruker 300 MHz instrument. They are reported as follows: chemical shifts δ in ppm, multiplicity, coupling constants J in Hz, number of protons, and assignment. All compounds were purchased from Merck and Alderich companies.

Preparation of Nano-Al_2O_3-SO_3H (NASA)

A 50 mL suction flask was equipped with a constant pressure and dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution of alkali trap. Nano alumina (1 g) was poured into the flask. Then a mixture of chlorosulfonic acid (1 mL, 15 mmol) in dry CH_2Cl_2 (3 mL) was also added drop wise over a period of 30 min at room temperature. The mixture was shaken for 1 h. After completion of the addition, the residual HCl was eliminated by suction. Then the mixture was washed with dry CH_2Cl_2. Finally, a white solid powder (2.2 g) was obtained [14].

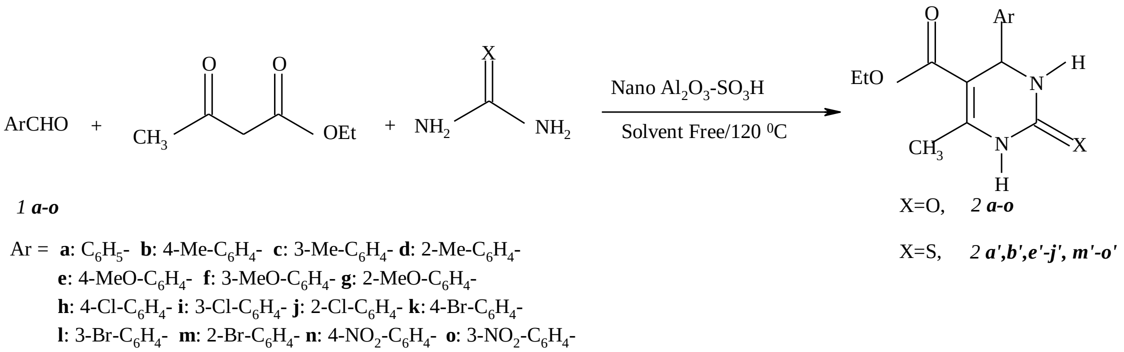
General Procedure for the Synthesis of 3,4-Dihydropyrimidine-2(1H)-Ones and Thiones

A mixture of benzaldehyde (**1a**), ethyl acetoacetate, urea or thiourea and NASA (0.05 g) (24–180 nm) as a catalyst were carried out under different conditions. (Scheme 1 and Table 1).

Table 1. NASA catalyzed synthesis of Biginelli-type product (**2a**) under different conditions.

Comp.	Amount of catalyst (g)	T (°C)	Solvent (mL)	Yield (%)[a]	Time (min)[b]
2a	With out	r.t.	Solvent-free	Trace	240
2a	With out	120	Solvent-free	Trace	60
2a	0.02	120	Solvent-free	15	30
2a	0.04	120	Solvent-free	65	15
2a	0.05	120	Solvent-free	92	5
2a	0.07	120	Solvent-free	91	10
2a	0.05	110	Solvent-free	88	20
2a	0.05	100	Solvent-free	80	35
2a	0.05	r.t.	H_2O (3)	Trace	60
2a	0.05	120	H_2O (3)	25	20
2a	0.05	r.t.	CH_3CN (3)	20	40
2a	0.05	120	CH_3CN(3)	30	35
2a	0.05	r.t.	EtOH (3)	20	40
2a	0.05	120	EtOH (3)	35	20
2p	0.05	120	Solvent-free	95	15

[a] Isolated yield; [b] Times are given after maximum progression of the reaction.



Scheme 1. The synthesis of Biginelli-type products in the presence of NASA as catalyst.

Table 2. Synthesis of 3,4-dihydropyrimidin-2(1*H*)- ones using NASA particles under solvent-free conditions at 120 ºC.

X=O			X=S		
Comp.	Time (min)	Yield (%)	Comp.	Time (min)	Yield (%)
2a	5	87	**2a'**	15	95
2b	16	90	**2b'**	60	75
2c	20	82	**2e'**	45	90
2d	35	76	**2f'**	16	90
2e	25	85	**2g'**	16	90
2f	17	87	**2h'**	30	77
2g	7	92	**2i'**	50	90
2h	7	90	**2j'**	40	70
2i	9	82	**2l'**	40	75
2j	10	75	**2n'**	90	90
2k	10	88	**2o'**	90	75
2l	16	80			
2m	12	78			
2n	6	90			
2o	7	87			

According to the data presented in Table 1, the best conditions were achieved as a mixture of the following materials as aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.2 mmol) and NASA (0.05 g) (24–180 nm) under solvent-free at a temperature of 120 °C. The progress of reaction followed by TLC using *n*-hexane/ethyl acetate (5:1) as an eluent until. Then the total disappearance of the ethyl acetoacetate was carried out. After cooling, the reaction to the room temperature and the separated solid were washed with cold water and then recrystallized from ethanol. All these products are known compounds, which were characterized by mp, Uv-vis, IR and ^{1}H-NMR spectra (Table 3).

Table 3. Melting point parameter of some 3,4-dihydropyrimidin- 2(1*H*)- ones.

Comp.	M.p (°C)	M.p (°C)	Comp.	M.p (°C)	M.p (°C)
	Observed	Reported [11]		Observed	Reported
2a	201-203	204-206	**2a'**	207-210	211-214 [13]
2b	211-214	212-215	**2b'**	188-191	191-193 [15]
2c	211-214	210-212	**2e'**	148-151	154-155 [13]
2d	207-210	208-209	**2f'**	152-154	150-152 [16]
2e	201-202	201-205	**2g'**	195-200	199-200 [17]

2f	207-209	207-208	**2h'**	172-175	176-177 [15]
2g	259-260	262-263	**2i'**	192-194	196-198 [16]
2h	209-211	210-212	**2j'**	116-118	118 [18]
2i	193-195	197-198	**2l'**	179-181	182-184 [19]
2j	216-218	218-219	**2n'**	106-109	110-112 [13]
2k	210-212	213-215	**2o'**	200-203	204-206 [20]
2l	190-193	196-197			
2m	198-200	205-207			
2n	207-209	207-208			
2o	223-225	226-227			

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(2a)**

UV/vis (CH_3CN), λ_{max} (log ε_{max}): 274.4 nm (4.01), 228.6 (3.91). IR, $\tilde{\nu}$ / cm^{-1}: 1720 ($CO_2C_2H_5$), 1700 (2-CO), 1640 (C=C). ^1H NMR (DMSO-d_6), δ: 1.08 (t, 3H, J = 7.07 Hz, OCH_2CH_3), 2.24 (s, 3H, CCH_3), 3.97 (q, 2H, J = 7.07 Hz, OCH_2CH_3), 5.14 (d, J = 3 Hz, 1H, CCHNH), 7.22–7.34 (m, 5H, Ar), 7.72 (s, 1H, NH), 9.17 (s, 1H, NH).

Ethyl 6-methyl-4-(4-nitrophenyl)-1,2,3,4-tetrahydropyrimidin-2(1H)-2-thione-5-carboxylate **(2n′)**

UV/vis (CH_3CN), λ_{max} (log ε_{max}): 285 nm (3.46), 230 (3.22). IR, $\tilde{\nu}$ /cm^{-1}: 3234 (N–H), 3110 (N–H), 2942 (CH), 1670 (C=O), 1580 (NO_2), 1340 (NO_2); ^1H NMR (DMSO-d6): d 1.48 (t, J = 7.2 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 4.23 (q, J = 7.2 Hz, 2H,CH_2), 5.74 (s, 1H, CH), 7.12 (s, 1H, NH), 7.48–8.35 (m, 4H, Ar–H), 8.41 (s, 1H, NH.

Results and discussion

Characterization of the catalyst

The morphology and particle size of NASA catalyst were investigated by TEM and SEM (Figure 1). The TEM images show some differences between nano alumina and NASA. The particle size of catalyst increases from 24 to 180 nm after treatment, which is due to the presence of SO_3H group on the spherical structure of nano alumina.

This reaction was carried out smoothly under solvent-free condition, using less an amount of NASA catalyst (0.027 mol%) when compared to an amount of catalyst (15 mol%) that have been reported in the literature [16]. However, the synthesis of Biginelli-type compounds was completed under the new conditions in less than 1 hour. Table 2 shows the generality of the present protocol. This method works effectively using urea or thiourea with various aldehydes. Another advantage of this method is the rate of reaction up to 24 times faster than it was previously reported. Furthermore, the yields were significantly better in comparison with results reported in literature [16] (Tables 4, 5).

Table 4. Comparison of the results of NASA with Al_2O_3-SO_3H catalyst reported in literature [16].

Comp.	Ar	Time (min)	Yield (%)	Time (h)[a]	Yield (%)[a]
2a	C_6H_5-	5	87	2.1	88
2h	4-Cl-C_6H_4-	7	90	1.6	94
2a'	C_6H_5-	15	95	2.7	81
2f'	3-MeO-C_6H_4-	16	90	1.7	73
2i'	3-Cl-C_6H_4-	50	90	1.5	81
2n'	4-NO_2-C_6H_4-	90	90	2.5	83

a.Ref. [16]

Table 5. Comparison of the catalytic efficiency of NASA with that of reported catalysts in the synthesis of some 3,4-dihydropyrimidin-2(1*H*)-ones/thiones.

Entry	Comp.	Condition	Time	Yield (%)	Ref.
1	$TiCl_3OTf$-[bmim]Cl	Solvent-free	20-40 (min)	65-95	[11]
2	Nano ZrO_2	H_2O	1-6 (h)	55-90	[12]
3	Al_2O_3-SO_3H	Solvent -free	1.5-2.7 (h)	73-94	[16]
4	SiO_2-Cl	Solvent-free	3h	80-96	[21]
5	Uranyl acetate and succinimide sulfonic acid	Solvent-free	2-4 (h)	75-95	[22]

Conclusion

In summary, we have found a practical condensation procedure for the preparation of 3,4-dihydropyrimidinones catalyzed by NASA, which gives excellent yields of high purity. It has many other advantages, such as milder reaction conditions, shorter reaction time, and easy recovery of catalyst. Its performance has been compared with that of other heterogeneous base catalysts, such as HCl, silica gel/sulfonic acid catalyst (SiO_2–SO_3H) and nano ZrO_2. As a result, NASA is known to be a useful and interesting heterogeneous catalyst for base-induced organic reactions.

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