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Research Article

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Nano Mangnesium Aluminate catalyzed one-pot synthesis of 3,4-dihydro-2(*1H*)-pyrimidinones

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ABSTRACT

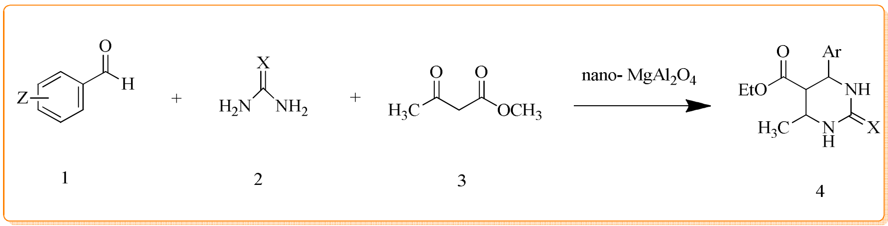
An efficient synthesis of 3,4-dihydro-2(1H)-pyrimidinones using Nano- $MgAl_2O_4$as the catalyst from an aldehyde, β-Keto ester, and urea under solvent-free conditions is described.

Keywords: Biginelli reaction, Dihydropyrimidinones, Nano- $MgAl_2O_4$, One-pot, Reusable

INTRODUCTION

During the last decade, multi – component reactions have increasingly became important in organic and medicinal chemistry as efficient and low- cost tools for combinatorial synthesis. Biginelli has reported a multi – component reaction of ethyl acetoacetate, benzaldehyde and urea to obtain dihydropyrimidinone (DHPM)[1]. The DHPM derivatives have attracted considerable interest in recent years due to promising activities az calcium channel blockers, antihypertensive, antibacterial, antitumor and anti-inflammatory agents [2-5]. The Biginelli reaction could be catalyzed by acids such as $H_3PMo_{12}O_4$, 12- tungstophosphoric acid, chloroacetic acid , CuI , $Fe(CF_3CO_2)$, CaF_2 , trichloroisocyanuric acid , $ZrCl_4$, NH_2SO_3H , Y $(NO_3)_3 . 6H_2O$ and Nano – $MgAl_2O_4$.

Magnesium aluminate, $MgAl_2O_4$ is a typical spinel material and it has also attracted growing interest in diverse applications such as refactory material, microwave dielectric and ceramic caoacitor , humidity sensors, catalyst or catalyst support, and structural material in fusion reactors. Plus, Magnesiun aluminate has a low density (3.58 g/cm^3), high meltingpoint (2135 ℃), good resistance against chemical attacks and excellent strength at extremely high temperatures [6].The synthesis of $MgAl_2O_4$ with specific characteristics such as chemical homogeneity, high purity, low particle size and uniform size distribution depends substantially on preparation methods. As such magnesium aluminate has been synthesized by various methods such as sol- gel, solid state, spray drying, co-precipitation, and freeze – drying. However, most of these are either complex or materials in a large scale as compared to the combustion or sol- gel synthesis. Moreover, other disadvantages include the necessity of nano-sized products. Generally ,smaller particle size results in higher surface area. Which is required for different catalytic applications.Hence , using a hybrid sol- gel combustion method at relating low temperature is a new and good approach to prepare nano sized magnesium aluminate particles suitable for application in the above – mentioned different fields especially the photocatalytic(Scheme 1).

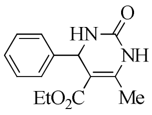
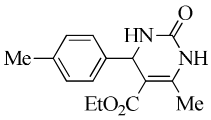
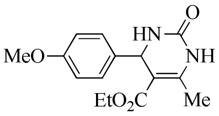
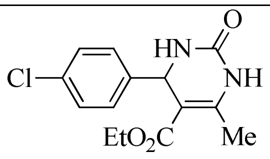
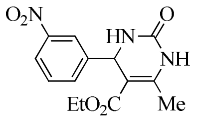
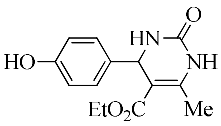
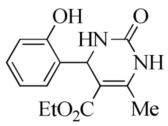


(Scheme 1)

RESULTS AND DISCUSSION

Results on the Biginelli reaction over $MgAl_2O_4$nano catalyst is presented in Table 1. It can easily be seen that the condensation of a series of aldehydes, 1,3-dicarbonyl compounds and urea orthiourea catalyzed by magnesium aluminate as an environmentally under solvent conditions at 80 ℃ and reaction completed within 1–1.5 h. The reaction occurred under water solvent condition and offered several advantages in preparative procedures, such as environmental compatibility, simpilifying work-up, formation of cleaner products, reduction of by products. This three component reaction proceeded smoothly and rapidly to give the corresponding dihydropyrimidinones in the presence of nano catalytic amount of $MgAl_2O_4$ in high yields (Table 1). As shown in Table 1, aromatic aldehydes containing both electron donating or withdrawing groups gave the desired products in good yields.

Table 1.$MgAl_2O_4$ catalyzed synthesis of dihydropyrimidinones

M.p/℃ Reported	M.p/℃ Observed	Yield (%)	Time (min)	product	Z	Entry
204-202	201-203	94	50	 4a	H	1
215-216	216-218	91	60	 4b	4-Me	2
202-204	202-204	93	60	 4c	4-OMe	3
212-214	211-213	96	50	 4d	4-Cl	4
229-231	230-232	95	40	 4e	$3-NO_2$	5
233-234	230-233	92	60	 4f	4-OH	6
200	200	92	60	 4g	2-OH	7

The yield of product in the presence of $MgAl_2O_4$is comparable with these catalysts. However, reaction in the presence of these catalysts, required longer reaction times than$MgAl_2O_4$. (Table 2)

Table 2.Comparison the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4a) using different catalysts

Entry	Catalyst	solvent	Yield (%)	Time(min)	References
1	$ZnCl_2$	Free	30-85	40-90	[7]
2	$HClO_4$- SiO_2	EtOH	81-96	15-40	[8]
3	$TiCl_4$	Free	45-90	50-90	[9]
4	Zeolite Y	EtOH	30-70	10-18h	[10]
5	$LaCl_3$	CH_3CN	80-91	105-120	[11]
6	$Fe(HSO_4)_3$	EtOH	47-98	180	[12]
7	Nano- $MgAl_2O_4$	H_2O	91-96	40-45	This work

Table 3.Checking the optimization of DHPM with different solvent:

Yield (%)	Time(min)	solvent	Entry
89	50	acetonitril	1
88	50	methanol	2
75	100	chloroform	3
90	50	ethanol	4
94	50	water	5

As you see in table 3, introducing water as the solvent, with the highest efficiency and best efficiency and minimum time is in this synthesis.

Table 4.The comparison of synthesis of 4a with the different amounts of catalyst

Yield(%)	Time(min)	The amount of $MgAl_2O_4$(g)	Entry
80	50	0.02	1
88	50	0.03	2
94	50	0.05	3
94	50	0.07	4

As can be seen in table 4, the right amount of 0.05g to 0.07g catalyst is not created with the large amounts of change in yield ,hence the amount of 0.05 Gram in this synthesis is more effective.

CONCLUSION

In summary, we have presented the nano- $MgAl_2O_4$ is an efficient, eco friendly and reusable catalyst for synthesis of Biginelli type compounds under solvent – free condition or sonication in ethylacetate. short reaction times, high yields, simplicity of operation, and easy work – up are some advantages of this method.

4. Experimental

4.1. General

The materials were purchased from Merck company and were used without any additional purification products were characterized by FT-IR, ^{1}H-NMR and comparison of their physical properties with those reported in the literature.

4.2. Typical procedures for the preparation of 3,4- dihydropyrimidinones in the presence of nano- $MgAl_2O_4$

A mixture of aldehyde(1 mmol), ethyl acetoacetate(1.3 mmol), urea(1 mmol), nano- $MgAl_2O_4$ (0.05g) and water as a solvent (5ml) was heated with stirring at 80℃. the progress of the reaction was monitored by TLC. After completion of reaction, the product was dissolved in hot methanol and filtered to recover the catalyst. the filtrate was concentrated to obtain the product. The crude product recrystallized from methanol.

4.2.1. Synthesis of 5-Ethoxycarbonyl- 4-phenyl-6-methyl -3,4-dihydropyrimidin-2(1H)-one (4a)

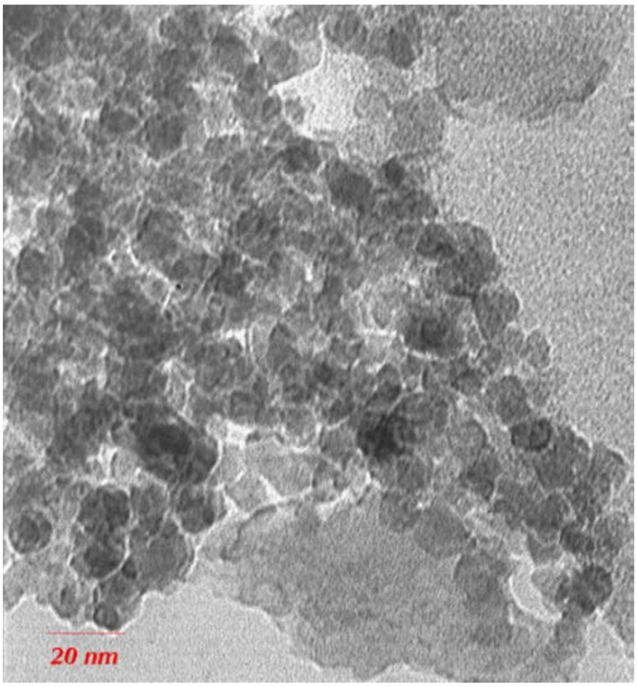
Mp 200-202 ºC; IR (KBr) (ν_{max}, cm^{-1}): 3244, 1724, 1639; δ_H/ppm (300 MHz, $CDCl_3$) 1.1 (3H, t, *J* 7.1 Hz, CH_3* CH_2O), 2.24 (3H, s, CH_3), 4.01 (2H, q, *J* 7.1 Hz, OCH_2), 5.16 (1H, s, CH), 7.21-7.30 (m, 5H, aromatic CH), 7.76 (s, 1H, NH), 9.24 (s, 1H, NH); *m/z* 260 (M^+).

4.2.2. Synthesis of 5-Ethoxycarbonyl- 4(4-methoxypheny)l-6-methyl -3,4-dihydropyrimidin-2(1H)-one (4c)

Yellow solid, Yield 98%; M.p. 82–84 oC; IR (neat): 1690, 1635 cm-1; 1H NMR (300 MHz, CDCl3): δ 1.21 (t, 3H, *J* = 7.2 Hz), 2.46 (s, 3H), 2.87 (s, 3H), 3.24 (s, 3H), 3.75 (s, 3H), 4.06–4.14 (m, 2H), 5.16 (s, 1H), 6.77–6.81 (m, 2H), 7.11–7.14 (m, 2H); 13C NMR (75 MHz, CDCl3): δ 14.3, 16.7, 31.1, 34.3, 55.3, 60.2, 60.4, 103.8, 113.9, 127.9, 133.2, 149.0, 153.8, 159.2, 166.1; HRMS, calcd.for C17H22N2O4 (M+) 318.1580, found 318.1577.

Preparation of nano-$MgAl_2O_4$

nano- $MgAl_2O_4$spinel was prepared by means of a procedure reported elsewhere (Navaei Alvar et al., 2010). In short, stoichiometric amounts of magnesium nitrate and aluminum nitrate and of the desired amount of hexadecyl-trimethyl-ammonium bromide (cetyltrimethylammonium bromide; CTAB) were added to well stirred deionised water. Then, ammonia solution was added dropwise to the well stirred slurry to adjust the pH value to around 9. After precipitation, the slurry was stirred for another 30 min and then refluxed at 80◦C for 24 h under continuous stirring. The mixture was then cooled to room temperature and filtered. The final product was dried at 100◦C for 24 h under flowing air and calcined at different temperatures.



TEM image of nano- $MgAl_2O_4$

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