



AN EFFICIENT SYNTHESIS OF 4-ARYL-SUBSTITUTED 3,4-DIHYDROPYRIMIDIN-2(1H)-ONES USING NANOCOMPOSITE FERRITE CATALYST

Vijaykumar M. Joshi^[a], Sanjay K. Vyawahare^[b], Sunil U. Tekale^[b], Sunita B. Shinde^[b], Mohammed Fareesuddin^[b], Satish A. Dake^[b], Suresh U. Shisodia^[b] and Rajendra P. Pawar^{[b]*}

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A simple and efficient protocol has been reported for the synthesis of 5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones using nanoparticulate ferrite composite as recyclable catalyst for one pot three component Biginelli reaction to afford the corresponding product in excellent yields.

* Corresponding Author

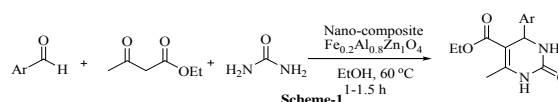
Fax: +91-240-2334430

E-Mail: rppawar@yahoo.com

[a] Shri Jagdishprasad Jhabarmal Timrewala University, Rajasthan, India

[b] Department of Chemistry, Deogiri College, Aurangabad-431 005, (MS) India.

Herein, we wish to report an efficient and versatile method for Biginelli reaction using nanocomposite ferrite material as a recyclable catalyst (**Scheme-1**).



Introduction

Multi-component reactions are the efficient tools in modern synthetic organic chemistry due to their significant features such as atom economy and straight forward reaction designing. Multicomponent reactions facilitate the synthesis of compounds of biological and pharmacological importance by introducing several steps in one pot reaction.

Biginelli reaction is an important multi-component reaction that allows one pot three component synthesis of 3, 4-dihydroxypyrimidin-2(1H)-ones and their analogues which exhibit many interesting pharmacological and biological properties. 3, 4-dihydropyrimidin-2(1H)-ones and their derivatives possess several biological activities such as antimicrobial [1], antifungal [2], anti-inflammatory [3], enzyme inhibitory [4], antihypertensive agents [5]. They also act as channel modulators and showed antagonist activities [6]. Thus Biginelli reaction is an important multi-component reaction for the synthesis of biologically active dihydropyrimidinone derivatives.

The first Biginelli reaction was reported by Pietro Biginelli in 1893 by the condensation of an aldehyde, β -keto ester and urea or thiourea in ethanol using a catalytic amount of HCl. This classical synthesis suffered from several drawbacks including low yields (25-60 %) and prolonged reaction time. To improve the reaction; numerous improvements were suggested by different researchers using different both acidic and basic catalytic systems such as copper (II) sulfamate [7], ClSO_3H [8], EPZ10 [9], InBr_3 [10], $\text{Pb}(\text{NO}_3)_2$ [11], NaIO_4 [12], $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ [13], Lanthanide Triflate [14], Sulfated Zirconia [15], Zeolite [16], Benzyltriethylammonium chloride [17], Ionic liquid [18], Microwave [19] etc. However, all these methods have several shortcomings which need to be modified.

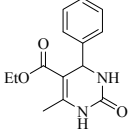
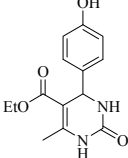
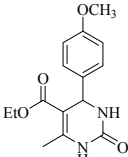
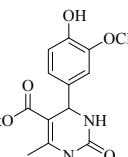
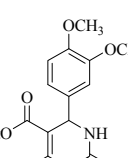
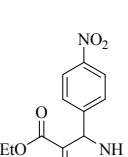
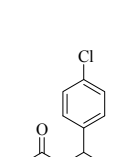
Experimental

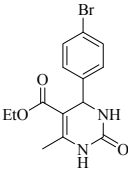
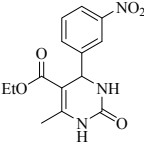
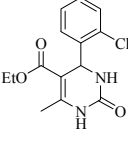
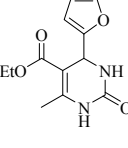
Chemicals were purchased from SD fine chemicals Ltd and used without further purification. Melting points of products were measured in open capillaries. NMR spectra were recorded 400 MHz Varian NMR spectrophotometer using tetramethylsilane (TMS) as the internal standard. All solvents were AR grade and used as received. IR spectra of the samples were recorded on Perkin IR spectrophotometer using KBr discs. Samples were scanned for mass on Shimadzu mass analyzer. The catalyst was synthesized by reported sol-gel method [20]

General procedure for the nanocomposite ferrite catalyzed synthesis of 4-aryl substituted 3, 4-dihydropyrimidin-2(1H)-ones

A mixture of aldehyde (2 mmol), ethyl acetoacetate (2 mmol), urea (3 mmol), ferrite nanocomposite $\text{Fe}_{0.2}\text{Al}_{0.8}\text{Zn}_1\text{O}_4$ (10 mol %) and 2 drops HCl in ethanol (5 mL) was heated at 60 °C for 1 hr. The progress of reaction was monitored by Thin Layer Chromatography (30 % ethyl acetate: hexane). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with hot ethanol (10 mL), filtered off to separate the catalyst. The filtrate was concentrated and the product was purified by recrystallization from ethanol. Using these conditions a series of different 3, 4-dihydropyrimidin-2(1H)-ones were obtained (**Table 1**). All the synthesized compounds are reported and characterized by IR, ^1H NMR, Mass and comparison of their physical constants as reported in the literature. The spectral data of representative compounds is described below:

Table 1: Synthesis of 4-aryl substituted 5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-ones using nanoparticulate composite ferrite catalyst.

Sr. No.	Ar	Product	Time, h	Yield, %	M. p., °c	Reference
1	C ₆ H ₅		1.30	92	205-207	[17]
2	4-OH-C ₆ H ₄		1.35	94	221-222	[7]
3	4-OCH ₃ -C ₆ H ₄		1	92	198-200	[17]
4	4-OH-3-OCH ₃ -C ₆ H ₃		1.45	91	257-259	[7]
5	3,4-(OCH ₃) ₂ -C ₆ H ₃		1.15	88	172-173	[17]
6	4-NO ₂ -C ₆ H ₄		1	87	209-211	[8]
7	4-Cl-C ₆ H ₄		1.2	92	211-213	[8]

8	4-Br-C ₆ H ₄		1.5	92	212-214	[13]
9	3-NO ₂ -C ₆ H ₄		1.2	90	2085-201	[13]
10	2-Cl-C ₆ H ₄		1.2	94	213-215	[9]
11	2-Furyl		1.2	89	208-210	[10]

Yield of reactions using aldehyde (2 mmol), ethylacetoacetate (2mmol), urea or thiourea (3 mmol), nanocomposite ferrite (10 mol %) and 2 drops HCl in ethanol (5 mL) at 60 °C temperature.

5-Ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (Entry 2, Table 1). M.p. 221-222 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 1.6 (t, 3H), 1.9 (s, 3H), 4.65 (q, 2H), 5.05 (s, 1H), 5.8 (s, 2H), 5.5 (s, 1H), 6.6 (d, 2H), 7.05 (d, 2H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 23.123, 24.011, 29.726, 50.001, 62.584, 117.356, 121.814, 127.645, 136.015, 145.143, 153.468, 169.542; IR (KBr) cm⁻¹ 3383, 3236, 2920, 1627, 1516, 1447.

5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (Entry 3, Table 1) M.p. 198-200 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 1.15 (t, 3H), 2.29 (s, 3H), 3.72 (s, 3H), 4.05 (q, 2H), 5.28 (s, 1H), 6.20 (brs, 1H, NH), 6.84 (d, 2H), 7.21 (d, 2H), 8.75 (brs, 1H, NH); ¹³C NMR (100 MHz, CDCl₃): δ ppm 14.404, 16.742, 55.47, 60.18, 67.301, 101.723, 114.154, 128.039, 136.494, 146.399, 154.021, 159.421, 165.365; IR (KBr) cm⁻¹ 3276, 3112, 2979, 2826, 1614, 1512, 1720, 1653, 1463, 1082, 842.

Results and Discussion

To find out the utility of catalyst, a mixture of 1 equivalent amount of 4-methoxybenzaldehyde, ethyl acetoacetate and 1.5 equivalent urea in water were refluxed for 10 h with different catalysts. Different catalysts such as HCl, CuCl, CuCl₂, and ferrite composite

were used to explore the reaction. After 10 h, the crude product was diluted with 5 mL ethanol and filtered off to separate the catalyst. The filtrate was concentrated and the product was purified by recrystallization in ethanol. The results are presented in **Table 2** which shows that Ferrite Composite was the best among tested catalysts, but the yields were not so high.

To check the temperature effect on the formation of product, these reactions were carried out at different temperature (**Table 3**). The maximum yield of product was obtained at temperature 60 °C. Thus, the best results were obtained using 10 mol% of the nanocomposite catalyst ferrite in ethanol at 60 °C temperature.

Table 2. Effects of the Catalysts on the formation of 4-methoxyphenyl 5-ethoxycarbonyl-6-methylpyrimidin-2(1H)-ones

Entry	Catalyst	Amount	Yield, % ^b [Ref.]
1	Free	----	39
2	HCl	1 ml	44 [21]
3	CuCl	10 mol%	63 [21]
4	CuCl ₂	10 mol%	71 [21]
5	Ferrite composite	10 mol%	92

^aReaction conditions: 4-methoxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol), ferrite composite (10 mol %) and 1 drop HCl in ethanol (2 mL), ^bIsolated yield.

Table 3. Effects of temperature on the formation of 4-methoxyphenyl-5-ethoxycarbonyl-6-methylpyrimidin-2(1H)-ones

Entry	Temperature, °C	Time, min	Yield, % ^b
1	RT	60	--
2	40	60	18
3	50	60	24
4	60	60	92
5	60 and above	60	94

^aReaction conditions: 4-methoxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol), nanocomposite ferrite catalyst (10 mol %) and 1 drop HCl in ethanol (1 mL); ^bIsolated yield.

Conclusion

In summary the present work explores a new approach for one pot three component Biginelli reaction using nano composite ferrite material as a heterogeneous catalyst in ethanol. This protocol shows several advantages, such as shorter reaction time, operational and experimental simplicity; making it an attractive process for Biginelli reaction.

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