SYNTHESIS OF 3,4-DIHYDROPYRIMIDINONES CATALYZED BY AMMONIUM CHLORIDE OR MONTMORILLONITE KSF WITHOUT SOLVENT UNDER ULTRASONIC IRRADIATION

Hela SLIMI [a], Younes MOUSSAOUI [a,b], Ridha BEN SALEM [a*]

[a] *Physical Organic Chemistry Laboratory, University of Sfax, Faculty of Science, 3018, Sfax, Tunisia. Tel: (+216) 74 276 400. Fax: (+216) 74 274 437. E-mail: Ridha.BenSalem@voila.fr*
[b] *Science Faculty of Gafsa, University of Gafsa, Zarroug City, 2112, Gafsa, Tunisia. E-mail: y.moussaoui2@gmx.fr*

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ABSTRACT: The condensation of aldehydes, β-ketoesters and urea catalyzed by ammonium chloride or montmorillonite KSF without solvent results dihydropyrimidinones. Under ultrasonic irradiation at room temperature, Biginelli products were obtained in higher yields with shorter reaction time.

Keys words: dihydropyrimidinones, ammonium chloride, montmorillonite KSF, ultrasonic irradiation.

INTRODUCTION

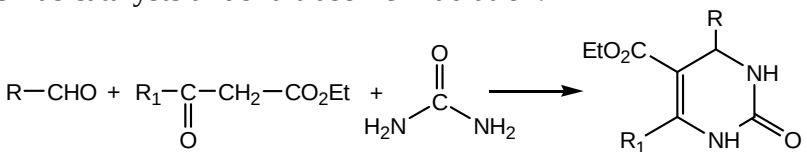
Dihydropyrimidinones and their derivatives represent a heterocyclic motif in the realm of natural and synthetic compounds of remarkable pharmacological efficiency. They exhibit wide spectrum of biological and therapeutic activities such as anti-tumor, anti-bacterial, anti-viral, anti-hypertensive and anti-inflammatory effects [1-6]. In addition, these compounds have emerged as integral backbones of several calcium channel blockers [4,7,8], α-1a-antagonists [9] and neuropeptide antagonists [4]. As result of their medicinal properties, synthesis of the dihydropyrimidinones has received much attention in finding a versatile and simple process for preparing these compounds under very mild conditions. The most simple and straight forward procedure, reported by Biginelli, involves three component, one-pot condensation of a β-ketoester, an aldehyde and urea or thiourea under strong acidic condition [10]. However, this reaction requires long reaction times and harsh conditions and often suffers from low yields of products particularly when substituted aromatic and aliphatic aldehydes are employed [10-12]. This has led to the disclosure of several methodologies for the synthesis of dihydropyrimidinones derivatives using ionic liquids [13], lanthanide triflates [14], lanthanide chloride [15], indium chloride [16], $ZrCl_4$ [17], $(NH_4)_2PO_4$ [18], TMSCl [19], TMSi [20], $InBr_3$ [21], $FeCl_3$ [22], LiBr [23], VCl_3 [24], $TaBr_5$ [25], PPh_3 [26], silica chloride [27], HCOOH [28], ultrasonic irradiation [29,30] and microwave irradiation [31,32]. However, many of these methods suffer from drawbacks such as the use of expensive reagents and long reaction times. Recently, sonochemistry as a new trend in organic chemistry has offered a versatile and more environmentally friendly conditions for a large variety of syntheses. Thus, a large number of organic reactions can be carried under ultrasonic irradiation in high yields, short reaction times and mild conditions [33-37]. Moreover, solvent free organic syntheses have received considerable attention because they are non pollutant, efficient and highly selective [38].

In view of our interest in the development of clean chemical processes, we report an environmentally procedure for the synthesis of dihydropyrimidinones without solvent under ultrasonic irradiation.

* Corresponding author, e-mail : ridha.bensalem@voila.fr

RESULTS AND DISCUSSION

Dihydropyrimidinones were synthesized by simple one-pot, three component, Biginelli condensation of an aldehyde, β-ketoester and urea without solvent using ammonium chloride, Montmorilonite KSF as catalysts under ultrasonic irradiation.



Scheme 1: Synthesis of dihydropyrimidinones via Biginelli reaction.

Table I: Yields of dihydropyrimidinones.

R	R_1	Product	Yields (%)				
			M1	M2	M3	M4	M5
C_6H_5	CH_3	1	74	92	80	95	94
4HO-C_6H_4	CH_3	2	66	84	86	94	94
4MeO-C_6H_4	CH_3	3	61	85	79	93	92
4Cl-C_6H_4	CH_3	4	56	83	77	94	95
4Me-C_6H_4	CH_3	5	55	82	76	94	92
4NO_2-C_6H_4	CH_3	6	54	82	78	90	89
CH_3	CH_3	7	26	40	55	43	50
C_2H_5	CH_3	8	30	63	70	62	66
C_3H_7	CH_3	9	30	70	74	73	76
C_4H_9	CH_3	10	32	70	86	74	85
C_6H_5	C_2H_5	11	44	88	76	84	85
4HO-C_6H_4	C_2H_5	12	58	75	76	82	84
4MeO-C_6H_4	C_2H_5	13	32	84	75	83	80
4Cl-C_6H_4	C_2H_5	14	55	80	70	80	82
4Me-C_6H_4	C_2H_5	15	60	76	68	78	80
4NO_2-C_6H_4	C_2H_5	16	42	75	66	80	82
CH_3	C_2H_5	17	25	50	51	50	52
C_2H_5	C_2H_5	18	31	52	50	54	53
C_3H_7	C_2H_5	19	32	54	48	62	60
C_4H_9	C_2H_5	20	32	56	50	70	72

M1: Aldehyde (10mmol); urea (15mmol); β-ketoacetate (10mmol); EtOH (20mL); HCl; reflux for 18 hours.
M2: Aldehyde (10mmol); urea (15mmol); β-ketoacetate (10mmol); NH_4Cl (4mmol); 100°C; 3 hours.
M3: Aldehyde (10mmol); urea (15mmol); β-ketoacetate (10mmol); KSF (0.5g); 100°C; 3 hours.
M4: Aldehyde (10mmol); urea (15mmol); β-ketoacetate (10mmol); NH_4Cl (4mmol); ultrasonic irradiation; 40min.
M5: Aldehyde (10mmol); urea (15mmol); β-ketoacetate (10mmol); KSF (0.5g); ultrasonic irradiation; 40min.

The results in table I indicate that Montmorillonite KSF and ammonium chloride showed catalytic reactivity for Biginelli reaction. Montmorillonite KSF has many advantages such as ease of handling, low cost and use of an environmentally-friendly catalyst. Montmorillonite KSF could be recovered by filtration and reused with similar reactivity after washing with hot ethanol or methanol and heating at 115°C for 6 hours. The results are in agreement with those of Bigi [39]. Indeed, ammonium chloride seems to be an excellent catalyst for the one-pot, three component, Biginelli

condensation under solvent free conditions to afford the corresponding 3,4-dihydropyrimidinones in high yields at 100°C.

The reaction consists in several successive steps with formation of two intermediates: acylimine resulting from reaction of urea with aldehyde, and the enol resulting from enolisation of β-ketoacetate. A condensation between these intermediates produces the cyclic transient intermediate which, by elimination of water, gives the dihydropyrimidinone [40].

The reactivity of aromatic aldehyde in the Biginelli reaction is better than aliphatic aldehydes. Furthermore, aromatic aldehydes, carrying either electron-donating or electron-withdrawing substituents, all reacted very well, giving excellent yields. The electronic effect and nature of the substituent on the aromatic aldehyde did not show any remarkable effect in terms of yields. The comparison of reaction time and yield with or without ultrasonic conditions show that the ultrasonic irradiation accelerates the Biginelli reaction.

The solvent-free condition facilitated the Biginelli condensation. Under ultrasonication and solvent free condition, dihydropyrimidinone derivatives were obtained similar to or higher yields than those obtained without ultrasonic irradiation. The main advantage of ultrasonic application is the decrease in reaction time. It is presumably because the ultrasonic irradiation provides the energy for the transition state of the reaction [41]. This is due to cavitation, a physical process that creates enlarges, thus enhances the mass transfer [42,43] and allows chemical reactions to occur. Indeed, the creation of the hot spots in the reactional medium intense local temperatures and high pressures [44]. However, very reactive chemical species are produced, with a short time, giving the corresponding dihydropyrimidinones.

In conclusion, we have reported the synthesis of dihydropyrimidinones by simple one-pot, three component, Biginelli condensation of an aldehyde, β-ketoester and urea catalyzed by ammonium chloride or montmorillonite KSF under solvent-free conditions. The obtained results show that montmorillonite KSF can be reused after recovery with similar reactivity. The use of ultrasonic irradiation at room temperature improved the Biginelli reaction yielding the products in good to excellent yields within 40 minutes. Ultrasonic irradiation offers several significant advantages over conventional method including higher yields, milder conditions, higher purity and shorter reaction times.

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Experimental:

Procedure M1: A mixture of aldehyde (10 mmol), β-ketoacetate (10 mmol), urea (15 mmol) and conc. HCl (2 mL) in ethanol (20 mL) was heated under reflux for 18 h. After cooling, the reaction mixture was poured into crushed ice. The product was filtered, washed with cold water and a mixture of ethanol/water then dried. The crude solid products were recrystalized from ethanol or ethylacetate/n-hexane.

Procedure M2: A mixture of aldehyde (10 mmol), β-ketoacetate (10 mmol), urea (15 mmol) and ammonium chloride (4 mmol) are introduced into a round-bottomed flask equipped with a cooling device. The reaction mixture was heated with stirring at 100°C for 3h. The product was filtered, washed with water. The crude solid products were recrystallized from ethanol.

Procedure M3: A mixture of aldehyde (10 mmol), β-ketoacetate (10 mmol), urea (15 mmol) and KSF (0.5g) are introduced into a round-bottomed flask equipped with a cooling device. The reaction mixture was heated with stirring at 100°C for 3h. The product was filtered, washed with water. The crude solid products were recrystallized from ethanol.

Procedure M4: Aldehyde (10 mmol), β-ketoacetate (10 mmol), urea (15 mmol), NH_4Cl (4 mmol) were mixed in a 50 mL conical Pyrex flask. The ultrasonic probe was immersed directly in the reactor. An

ultrasonic generator (sonics VC 505 300 W) emits the sound vibration into the reaction mixture. Sonification was achieved at low frequencies of 20 kHz (amplitude of 50%) at room temperature for 40 minutes. After completion of the reaction, the resulting suspension was filtered. The collected solid was washed with water and ethanol, and then dried. The pure product was obtained by recrystallization from ethanol.

Procedure M5: The same protocol as in procedure (M_4), but with KSF (0.5g) instead of ammonium chloride.

Recording of spectra

^{1}H (300MHz) and ^{13}C (75MHz) NMR spectra are recorded on a Bruker spectrometer in DMSO-d_6, with tetramethysilane as internal reference.

The products were analysed by GC–MS (Hewlett–Packard computerised system consisting of a 5890 gas chromatograph coupled to a 5971A mass spectrometer) ionisation mode used was electronic impact at 70 eV. Microanalyses were performed using a C, H, N Analyzer Model 185 from Hewlett-Packard. IR spectra are recorded in KBr on a Bruker Tensor 27 spectrometer in the range 4000-400cm^{-1}.

All the products were confirmed by comparing their melting points, IR, ^{1}H NMR and ^{13}C NMR data with literature data [45-47].

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