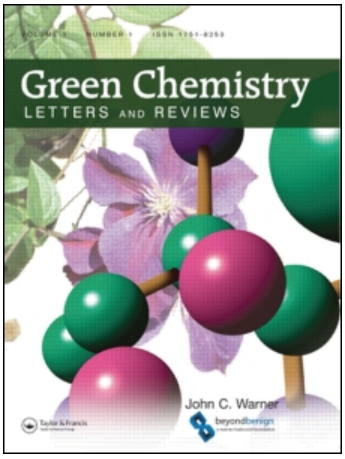

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RESEARCH LETTER

Synthesis of 3,4-dihydropyrimidinones in the presence of water under solvent free conditions using conventional heating, microwave irradiation/ultrasound

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An efficient, simple, and environmentally clean synthesis of 3,4-dihydropyrimidinones in excellent yields in the presence of water without additional solvent/acid catalyst under conventional heating, microwave irradiation/ultrasound is reported.

Keywords: water; Biginelli; green method; microwave; ultrasound

Introduction

Green or sustainable chemistry has become a subject of intensive research and the studies in this area have led to the development of cleaner and relatively benign chemical processes with many new technologies being developed in recent years (*1,2*). Among them, much effort has been devoted toward the replacement of toxic and volatile organic solvents with their safe alternatives including water, ionic liquids, supercritical fluids, immobilized solvents, fluorous solvents, and the use of solvent-less protocol (*3,4*). Water is the most desirable solvent for chemical reactions for the reasons of cost, safety, and environmental concerns (*5–11*) and its use under catalyst free conditions provides an excellent tool for achieving an eco-friendly and environmentally clean organic synthesis. Further the use of microwave irradiation or ultrasound is a step forward in this direction, which can offer many advantages such as high yields, enhanced reaction rates, and shorter reaction times due to their uniform heating effect. 3,4-Dihydropyrimidinones (DHMPs) denoted as Biginelli compounds constitute an important class of organic compounds which possess diverse therapeutic and pharmacological properties including antiviral, antitumor, antibacterial, and anti-inflammatory activities (*12,13*). Furthermore, these compounds have emerged as calcium channel blockers, antihypertensive agents, and α-1a-adrenergic antagonists. Moreover, several alkaloids and natural products containing the dihydropyrimidine core have been found to exhibit interesting biological properties. Thus the synthesis of this biologically important heterocyclic nucleus is of great importance and in this context a variety of improved methodologies have been reported using Lewis acids as well as protic acids as promoters (*14–27*). In spite of their potential utility most of the existing methods suffer from certain drawbacks, such as use of expensive reagents, toxic and volatile solvents, strong acidic conditions, stoichiometric amount of catalyst, homogeneous conditions, longer reaction times, unsatisfactory yields, and incompatibility with other functional groups. Recently developed methods using microwave irradiation, ultrasound, solvent-less protocol, and polymer supported reagents have made further improvements (*28–35*), albeit involving the use of toxic and expensive transition metals, concentrated HCl as catalysts, high reaction temperature, or requiring sealed reaction vessels. In the present letter, we wish to report an efficient, simple and green water assisted protocol for the synthesis of medicinally important 3,4-DHMPs in excellent yields without additional solvent/acid catalyst under conventional heating, microwave irradiation, or ultrasound (Scheme 1).

At first, we studied the Biginelli condensation of a variety of aldehydes both aromatic and heterocyclic by taking the aldehyde, β-dicarbonyl compound, urea, and water (3–4 drops) into a 25 ml round bottomed flask. The resulting suspension was stirred at 80°C without additional solvent/acid catalyst under conventional heating. The mixture became solidified at the end of the reaction, which was crushed and added into water. The products were isolated by

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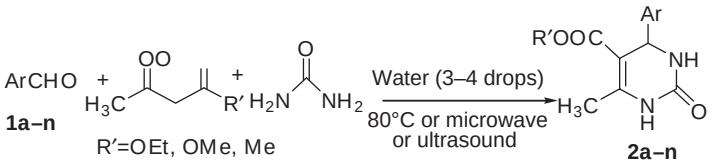

2a, Ar=Ph, R′=OEt
2b, Ar=4-$CH_3C_6H_4$, R′=OEt
2c, Ar=4-$CH_3OC_6H_4$, R′=OEt
2d, Ar=4-$NO_2C_6H_4$, R′=OEt
2e, Ar=4-ClC_6H_4, R′=OEt
2f, Ar=2-ClC_6H_4, R′=OEt
2g, Ar=2-pyridyl, R′=OEt
2h, Ar=2-Furyl, R′=OEt
2i, Ar=C_6H_5CH=CH, R′=OEt
2j, Ar=C_6H_5, R′=OMe
2k=Ar=4-$NO_2C_6H_4$, R′=OMe
2l, Ar=4-$CH_3OC_6H_4$, R′=Me
2m, Ar=4-ClC_6H_4, R′=Me
2n, Ar=C_6H_5, R′=Me

Scheme 1. Synthesis of dihydropyrimidinones.

filtration and purified via recrystallization using ethanol. All the substrates were efficiently converted into corresponding 3,4-DHMPs in high yields. These results are presented in Table 1. To examine the effect of microwave/ultrasound, we further studied the Biginelli condensation of various aldehydes, β-dicarbonyl compounds, and urea using water as a promoter under described reaction conditions and the results are summarized in Table 1. While the reaction was found to be very fast and completed within 2 min under microwave irradiation, it was found to be faster in comparison to conventional heating with the use of ultrasound. To evaluate the effect of water, we carried out blank reaction between 4-chlorobenzaldehyde, urea, and ethylacetoacetate without water using conventional heating, microwave irradiation/ultrasound under similar reaction conditions. In the case of conventional heating, the reaction proceeded slow without water and required longer reaction time (2.0 h), however, in microwave irradiation the reaction did not proceed even after prolonged reaction time. In ultrasound, the reaction was found to be very slow and afforded a lower product yield (Table 2, entry 1). We assume that in the present method water probably facilitates the formation of acylimine intermediate generated from the reaction of aldehyde, and urea through hydrogen bonding between carbonyl oxygen of aldehyde and NH hydrogen of urea. From the mechanistic viewpoint (*36*), the generation of acylimine intermediate is the key step in Biginelli condensation, which subsequently reacts with β-dicarbonyl compound followed by cyclodehydration to give

Table 1. Synthesis of 3,4-dihydropyrimidinones.[a]

		Conventional[b]		Microwave[c]	Ultrasound[d]	
Entry	Product **2**	*t* (min)	Yield[e]	Yield[e]	*t* (min)	Yield[e]
1	2a	45	92	98	30	96
2	2b	45	94	96	30	95
3	2c	50	90	96	35	92
4	2d	60	89	97	40	92
5	2e	65	90	96	40	94
6	2f	60	90	95	40	94
7	2g	55	80	88	35	85
8	2h	60	80	90	35	90
9	2i	75	92	90	50	82
10	2j	55	90	92	40	90
11	2k	60	92	95	35	94
12	2l	65	92	89	40	86
13	2m	60	90	90	35	87
14	2n	75	90	92	40	90

[a]Reaction conditions: aldehyde (2 mmol); urea (2 mmol); β-dicarbonyl compound (2 mmol); and water (3–4 drops).
[b]Heating at 80°C.
[c]Microwave irradiation (750 W, reaction time 2 min).
[d]Ultrasound irradiation (25 kHz).
[e]Isolated yields.

Table 2. Biginelli reaction using other protic solvents as promoter.[a]

		Conventional[b]		Ultrasound[c]	
Entry	Solvent	*t* (min)	Yield[d]	*t* (min)	Yield[d]
1[e]	–	120	80	60	30
2	EtOH	70	90	60	40
3	MeOH	80	87	60	42
4	iPrOH	80	85	60	40

[a]Reaction conditions: 4-chlorobenzaldehyde (2 mmol); urea (2 mmol); ethylacetoacetate (2 mmol); and solvent (0.5 ml).
[b]Refluxing.
[c]Ultrasonic irradiation (25 kHz).
[d]Isolated yields.
[e]Blank experiment.

corresponding 3,4-DHMPs. To establish the effect of hydrogen bonding in promoting the reaction, we carried out the Biginelli condensation between 4-chlorobenzaldehyde, ethylacetoacetate, and urea in presence of other protic solvents like ethanol, methanol, and isopropanol. In all cases, reaction proceeded well under conventional heating and afforded comparable product yield within nearly similar reaction times (Table 2). It is also worth mentioning that under ultrasonic irradiation, the reaction was found to be very slow and yielded product in poor yield, however, in case of microwave, the reaction did not proceed in ethanol, methanol, and isopropanol under similar reaction conditions. This fact established the key role of water as a promoter for this reaction under microwave/ultrasound irradiation. Further, Biginelli condensation of 4-chlorobenzaldehyde, ethylacetoacetate, and urea in the presence of a mixture of ethanol and water (1:1) under conventional heating, microwave irradiation/ultrasound was found to be very slow and afforded poor product yield in longer reaction time. This might be due to the strong coordination of water with ethanol rather than aldehyde. The present method uses only water as a promoter without additional solvent/acid catalyst, produces no waste, shows significant enhancement in reaction rates under microwave irradiation and therefore represents a green and enviro-economic synthetic methodology for the Biginelli condensation.

In summary, we have developed a green and environmentally benign water assisted protocol for the synthesis of 3,4-DHMPs in excellent yields without using additional solvent/acid catalyst under conventional heating, microwave irradiation/ultrasound. The presence of water was found to be vital and the reactions were found to be faster under microwave irradiation/ultrasound in comparison to conventional heating and afforded products in high yields.

Experimental

All the substrates and solvents were commercially available and purified before use. Experiments were carried out in Milestone START Microwave lab station and ultrasonic processor used was Hielscher Ultrasound Technology UP2005.

General experimental procedure

A 25 ml round bottomed flask was charged with aldehyde (2 mmol), urea (2 mmol), β-dicarbonyl compound (2 mmol), and 3–4 drops of water. The resulting suspension was stirred at 80°C under conventional heating or microwave irradiation (750 W, 2 min). The mixture became solid at the end of the reaction, which was crushed and added into the water. The crude product was isolated by filtration that further purified by recrystallization with ethanol to afford pure 3,4-DHMPs. In case of ultrasonic irradiation, a small flask containing aldehyde (2 mmol), urea (2 mmol), β-dicarbonyl compound (2 mmol), and water (3–4 drops) was sonicated at 25 kHz for the time indicated in Table 1. The crude solid was subjected to usual workup to obtain pure product. All the products were isolated and their isolated yields are given in Table 1. Identity of the products was established by comparing their physical and spectral data with those of reported compounds (*37*).

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