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Biginelli reaction in aqueous medium: a greener and sustainable approach to substituted 3,4-dihydropyrimidin-2(1*H*)-ones

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Abstract—An environmentally benign aqueous Biginelli protocol for the synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones using polystyrenesulfonic acid (PSSA) as a catalyst has been achieved. These microwave-assisted reactions proceed efficiently in water in the absence of organic solvent, with simple filtration as the product isolation step.

Green chemistry is a rapidly developing new field that provides us a proactive avenue for the sustainable development of future science and technologies.[1] Green chemistry uses highly efficient and environmental benign synthetic protocols to deliver life saving medicines, accelerating lead optimization processes in drug discovery, with reduced unnecessary environmental impact. Green chemistry also offers enhanced chemical process economics concomitant with a reduced environmental burden. From this view point, it is desirable to use water instead of organic solvents as a reaction medium, since water is a safe, abundant and environmentally benign solvent.[2]

Dihydropyrimidinones are an important class of organic compounds, which show prominent biological activity and are normally prepared using Biginelli reaction.[3] A large number of reports are available in the literature for this protocol,[4] including a few examples of Biginelli reaction in water.[5,6] Very recently, Zumpe et al. used propane phosphonic acid anhydride as a catalyst.[7] Although yield is good, the main concern for this protocol is the separation of catalyst from product that requires column chromatography. Recently, we reported the polystyrenesulfonic acid (PSSA) catalyzed greener synthesis of 1,3-dioxanes[8a] and hydrazones[8b] in aqueous medium using microwave (MW) irradiation. In continuation of our green chemistry programme,[8] we decided to explore the use of polymer supported polystyrenesulfonic acid as a catalyst for the synthesis of various substituted 3,4-dihydropyrimidin-2(1*H*)-ones (Scheme 1) using Biginelli protocol in water.

During initial exploratory reactions, we studied the condensation of ethyl acetoacetate, 4-chloro benzaldehyde and urea in water under MW irradiation, to establish the feasibility of our strategy to 3,4-dihydropyrimidin-2(1*H*)-ones systems and to optimize the reaction conditions (Table 1).

First the reaction was tested without any catalyst under MW irradiation conditions in aqueous medium and no reaction (NR) was observed at 80 and 100 °C. The use of Lewis acid[9] and Nafion-H[10] afforded poor yields of the products whereas acetic acid (AcOH) gave moderate yield.[9,11] However, PSSA efficiently catalyzed this reaction and afforded high yields of the desired product (Table 1, entry 5).

Using these optimized reaction conditions, the scope and efficiency of this aqueous approach was explored for the synthesis of a wide variety of substituted 3,4-dihydropyrimidin-2(1*H*)-ones and results are summarized in Table 2.

Keywords: Biginelli reaction; 3,4-Dihydropyrimidin-2(1*H*)-ones; Polystyrenesulfonic acid (PSSA); Aqueous medium; Microwave irradiation; Greener; Sustainable.

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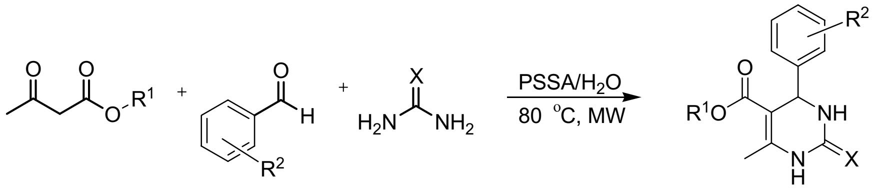


Scheme 1. Biginelli reaction in aqueous medium.

Table 1. Optimization of reaction conditions using MW irradiation

Entry	Catalyst	Solvent	Temperature (°C)	Reaction time (min)	Yield[ref] (%)
1	—	Water	80	30	NR
2	—	Water	100	30	NR
2	Ni $(NTf_2)_2$	Water	80	30	55[9]
3	Nafion-H	Water	80	30	50[10]
4	AcOH	Water	80	30	58[9,11]
5	PSSA	Water	80	20	91

All the aforementioned reactions (Table 2) proceeded expeditiously, delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing both, electron-donating and electron-withdrawing substituents; substrates with electron-withdrawing groups gave relatively higher yields. These three-component condensation reactions also proceeded smoothly with thiourea (Table 2, entries 11–15) and were complete within 20 min. In contrast, the reaction requires 5–6 h

Table 2. PSSA catalyzed synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones in water under MW irradiation

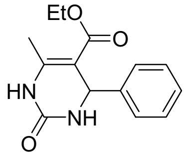
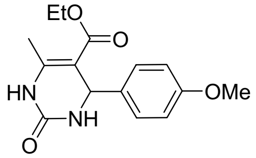
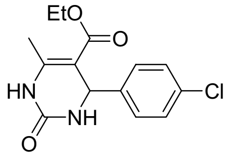
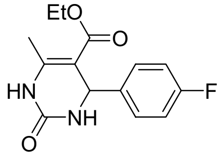
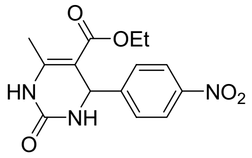
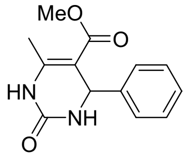
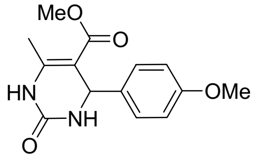
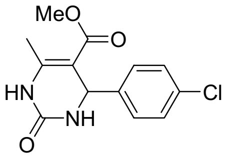
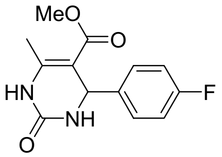
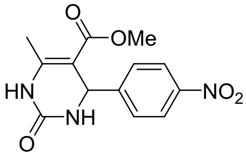
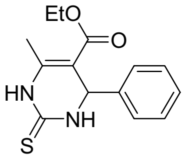
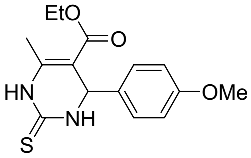
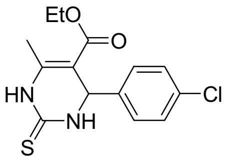
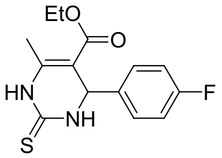
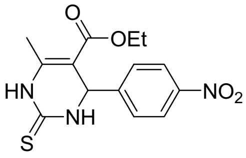
Entry	R^1	R^2	X	Product	Yield[a] (%)	References
1	Et	H	O		89	4e,7,11,12
2	Et	4-OCH_3	O		88	7,11,12
3	Et	4-Cl	O		91	7,11,12
4	Et	4-F	O		90	4e
5	Et	4-NO_2	O		88	4e,7
6	Me	H	O		88	11
7	Me	4-OCH_3	O		89	4e,12

Table 2 (*continued*)

Entry	R^1	R^2	X	Product	Yield[a] (%)	References
8	Me	4-Cl	O		92	11
9	Me	4-F	O		90	4e
10	Me	4-NO_2	O		89	4e,7
11	Et	H	S		87	4e,7,12
12	Et	4-OCH_3	S		87	4e,12
13	Et	4-Cl	S		88	11,12
14	Et	4-F	S		88	4e
15	Et	4-NO_2	S		86	4e,12

[a] Isolated yields. All the compounds are known in the literature and were characterized by ^{1}H NMR and MS.

for completion under conventional heating condition (oil bath). In all cases, the pure product was isolated by simple filtration, without any chromatography or cumbersome workup procedure.

It is noteworthy to mention that these reactions are working well in an aqueous medium without using any phase-transfer catalyst (PTC). This may be due to selective absorption of microwaves by polar molecules and intermediates in a multiphase system, which could substitute as a phase transfer catalyst,[13a] thereby providing the observed acceleration similar to that observed in ultrasound irradiation.[13b]

Thus, we have demonstrated an elegant protocol for the synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones using PSSA, which proceeds efficiently in water without use of organic solvent, under microwave irradiation.[14] Also the use of polymer supported, low toxic and inexpensive PSSA as a catalyst renders this method eco-friendly, with a very simple isolation procedure that entails the filtration of the precipitated products.

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14. *Typical experimental procedure*: The alkylacetoacetate (1 mmol), aldehyde (1 mmol) and urea/thiourea (1.2 mmol) were taken in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer, and were dissolved in 20% PSSA solution in water (three times the weight of aldehyde). The reaction tube was then placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 80 ± 5 °C (temperature monitored by a built-in infrared sensor), power 40–100 W and pressure 20–30 psi for 20 min. After completion of reaction, products were isolated with simple filtration (few ml of water was added to facilitate easy filtration) and recrystallized to afford pure 3,4-dihydropyrimidin-2(1*H*)-ones.