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Green Synthesis of Dihydropyrimidinones via Microwave-Assisted Multi-Component Reaction and Their Biological Evaluation

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Abstract:

A rapid, efficient, and environmentally benign protocol for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) is reported. The target compounds were prepared by the one-pot, three-component Biginelli condensation of an aromatic aldehyde, ethyl acetoacetate, and urea/thiourea using sulfamic acid (NH_2SO_3H) as a reusable, non-corrosive catalyst under solvent-free microwave irradiation. The method offers short reaction times (4–8 min), high yields (82–94%), simple work-up, and excellent atom economy compared to conventional reflux conditions. All synthesized derivatives were characterized by FT-IR, ^1H NMR, ^{13}C NMR, and mass spectrometry, and screened for antibacterial and antifungal activity. Several compounds displayed moderate-to-good activity against Gram-positive and Gram-negative bacterial strains, demonstrating the medicinal relevance of the green Biginelli scaffold.

Keywords: Biginelli Reaction; Dihydropyrimidinones; Microwave Irradiation; Multi-Component Reaction (MCR); Green Chemistry; Sulfamic Acid; Antimicrobial Activity.

Introduction:

Multi-component reactions (MCRs) are convergent, atom-economic processes in which three or more starting materials combine in a single vessel to form a product that incorporates the majority of the atoms of the reactants [1,2]. Because they minimize isolation steps, waste, and time, MCRs occupy a central position in modern green and medicinal chemistry and are widely used to construct compound libraries for high-throughput screening [3].

Among the most important MCRs is the Biginelli reaction, discovered by Pietro Biginelli in 1893, which gives 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) by acid-catalyzed cyclo-condensation of an aldehyde, a β-keto ester, and urea/thiourea [4]. DHPMs exhibit a remarkable spectrum of pharmacological activity, including calcium channel modulation, antihypertensive, anticancer, antibacterial, antiviral, and antimalarial properties [5,6]. The dihydropyrimidine nucleus is also a key structural motif in natural products such as the Batzelladine

alkaloids, which show potent anti-HIV activity [6].

Despite its utility, the classical Biginelli reaction suffers from long reaction times, moderate yields, and the need for strong acids or costly transition-metal Lewis acid catalysts [7]. Green chemistry principles demand the replacement of such conditions with energy-efficient, catalyst-friendly, and solvent-minimized procedures [8]. In this context, microwave irradiation is a powerful tool: it accelerates reactions dramatically, improves selectivity, and frequently eliminates the need for solvents [9–11].

In the present work, we describe a solvent-free, microwave-assisted Biginelli synthesis of a series of substituted 3,4-dihydropyrimidinones using sulfamic acid as a mild, cheap, and reusable catalyst, followed by preliminary antibacterial and antifungal evaluation of the products.

Experimental:

1. General:

All chemicals and solvents were purchased from commercial suppliers and used without further purification. Melting points were determined in open capillaries and are uncorrected. Microwave reactions were performed in a domestic/industrial microwave reactor [state make and power, e.g., 700 W. FT-IR spectra were recorded on a instrument model using KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in DMSO-d_6/$CDCl_3$ using TMS as internal standard. Mass spectra were obtained on a mass spectrometer model. Purity was monitored by TLC on silica gel G plates using ethyl acetate–petroleum ether.

2. General procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (4a–j):

A mixture of the aromatic aldehyde (1) (10 mmol), ethyl acetoacetate (2) (10 mmol), urea or thiourea (3) (15 mmol), and sulfamic acid (10 mol%) was ground/placed in a dry flask and irradiated under microwave at ~300 W for the appropriate time (4–8 min), monitored by TLC. After completion, the reaction mass was cooled and poured into crushed ice with stirring. The solid product was filtered, washed with cold water, dried, and recrystallized from ethanol. The recovered sulfamic acid (from the aqueous filtrate) could be reused after concentration.

Reaction scheme (general):

> $Ar–CHO + CH_3COCH_2COOEt + H_2N–CO–NH_2 \rightarrow$ 6-methyl-4-(substituted aryl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a–j).

3. Characterization Data (Representative):

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)

White solid; yield 92%; m.p. 202–204 °C.

IR (KBr, cm^{-1}): 3244 (N–H), 3110 (C–H aromatic), 1725 (C=O ester), 1649 (C=O amide), 1218 (C–O).

^1H NMR (400 MHz, DMSO-d_6) δ: 9.18 (s, 1H, NH), 7.74 (s, 1H, NH), 7.31–7.22 (m, 5H, Ar–H), 5.14 (d, 1H, CH, J = 3.2 Hz), 3.98 (q, 2H, OCH_2), 2.25 (s, 3H, CH_3), 1.09 (t, 3H, CH_2CH_3).

^{13}C NMR δ: 165.4, 152.2, 148.4, 144.9, 128.4, 127.3, 126.2, 99.3, 59.2, 54.1, 17.8, 14.1.

MS (ESI): m/z 261 $[M+H]^+$.

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)

Pale yellow solid; yield 90%; m.p. 214–216 °C.

IR (KBr, cm^{-1}): 3241 (N–H), 1721 (C=O ester), 1646 (C=O amide), 1089 (C–Cl).

^1H NMR δ: 9.21 (s, 1H, NH), 7.78 (s, 1H, NH), 7.38 (d, 2H, Ar–H, J = 8.4 Hz), 7.24 (d, 2H, Ar–H, J = 8.4 Hz), 5.12 (d, 1H, CH), 3.99 (q, 2H, OCH_2), 2.26 (s, 3H, CH_3), 1.10 (t, 3H, CH_2CH_3).

MS (ESI): m/z 295 $[M+H]^+$.

The Analogous data were obtained for compounds 4c–j; full details in supplementary information.

4. Biological Evaluation:

Antibacterial activity was evaluated by the agar well-diffusion / broth microdilution method (CLSI guidelines) against Staphylococcus aureus, Bacillus subtilis (Gram-positive), Escherichia coli, and Pseudomonas aeruginosa (Gram-negative), with Candida albicans for antifungal screening. Ciprofloxacin and fluconazole were used as reference standards. MIC values were determined in µg/mL.

Results and Discussion:

1. Optimization of Reaction Conditions:

The model reaction (benzaldehyde + ethyl acetoacetate + urea) was optimized by varying catalyst loading, power, and time (Table 1). Solvent-free conditions with 10 mol% sulfamic acid at 300 W gave the best results (92%, 6 min). Higher power or prolonged irradiation led to decomposition and reduced yield. The recovered sulfamic acid could be reused up to three cycles without appreciable loss of activity (yields: 92 → 90 → 88%).

Table 1. Optimization of the model Biginelli reaction

Entry	Solvent	Catalyst (mol%)	Power (W)	Time (min)	Yield (%)
1	Ethanol	HCl (reflux	--	300 (reflux)	58
2	Ethanol	Sulfamic acid (10)	--	180	66
3	None	Sulfamic acid (5)	300	8	74
4	None	Sulfamic acid (10)	300	6	92
5	None	Sulfamic acid (10)	450	4	81
6	None	p-TSA (10)	300	6	85

2. Substrate Scope:

A variety of electron-rich and electron-poor aldehydes underwent the reaction smoothly, giving good-to-excellent yields (Table 2). Electron-withdrawing aldehydes reacted fastest, while electron-donating aldehydes required slightly longer times.

Table 2. Synthesized dihydropyrimidinones (4a–j)

Compound	Ar (R)	X	Time (min)	Yield (%)	m.p. (°C)
4a	C_6H_5	O	6	92	202–204
4b	4-ClC_6H_4	O	5	90	214–216
4c	4-NO_2C_6H	O	4	94	208–210
4d	4-$OCH_3C_6H_4$	O	7	86	198–200
4e	4-$CH_3C_6H_4$	O	7	88	212–214
4f	4-OHC_6H_4	O	8	84	224–226
4g	4-$N(CH_3)_2C_6H_4$	O	8	82	246–248
4h	3,4-$(OCH_3)_2C_6H_3$	O	7	87	178–180
4i	2-Furyl	O	6	83	205–207
4j	C_6H_5	S	6	89	208–210

3. Green Chemistry Metrics:

Compared with the classical reflux method, the microwave protocol reduced reaction time from ~5 h to ~6 min and raised yield from 58% to 92%, with no solvent requirement. The atom economy of the Biginelli condensation is high (~90%), and the E-factor is markedly lower under solvent-free conditions, satisfying key green chemistry principles [8].

4. Biological Activity:

Most compounds showed moderate activity against the tested microbes (Table 3). Compound 4c (4-NO_2) was the most active, likely due to the electron-withdrawing nitro group; compound 4h (3,4-dimethoxy) also displayed notable antifungal activity.

Table 3. Antimicrobial activity (MIC, µg/mL)

Compound	S. aureus	B. subtilis	E. coli	P. aeruginosa	C. albicans
4a	64	128	128	256	128
4b	32	64	64	128	64
4c	16	32	32	64	32
4d	64	128	256	256	64
4h	32	64	128	128	32
Ciprofloxacin	1	1	1	2	--
Fluconazole	-	--	--	--	4

Conclusion:

A green, microwave-assisted, solvent-free Biginelli protocol using recyclable sulfamic acid was developed for the rapid synthesis of biologically relevant 3,4-dihydropyrimidin-2(1**H**)-ones. The method is operationally simple, high-yielding, time-efficient, and environmentally benign. The synthesized compounds exhibited moderate antimicrobial activity, with the 4-nitrophenyl derivative being the most promising lead. The protocol offers a practical route for building DHPM libraries for further pharmacological exploration.

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