

AN EFFICIENT BRONSTED ACID-CATALYZED AQUEOUS BIGINELLI PROTOCOL FOR THE SYNTHESIS OF DIHYDROPYRIMIDINONE

S. S. Pawde¹, M. H. Gagare², S. S. Patil¹, D. B. Muley¹, and A. S. Patki^{3,✉}

¹Department of Chemistry, Shivaji Mahavidyalaya, Udgir-413517, Nanded (MS), India

²Department of Chemistry, Rajarshi Shahu Mahavidyalaya Latur-413512, India

³Department of Chemistry, Shivaji Mahavidyalaya Renapur-413527, India

✉Corresponding author: abhijeetpatki007@gmail.com

ABSTRACT

This study reports a highly efficient, sustainable, and step-economical approach for the synthesis of biologically relevant dihydropyrimidinones (DHPMs) via a multicomponent Biginelli reaction catalysed by sulfonated naphthalene formaldehyde (SNF) in an aqueous medium. Under optimised conditions (10 wt% SNF in water at 80 °C), an array of eleven structurally diverse DHPM derivatives was obtained in good to excellent yields (73–95%) within short reaction times. Beyond optimising operational metrics, this research directly addresses a persistent challenge in modern synthetic chemistry: reducing the discipline's heavy reliance on toxic, metal-based catalysts and hazardous volatile organic solvents. Eleven diverse DHPM derivatives were obtained in good to excellent yields. The water-soluble catalyst could be reused with slight activity loss, and the process highlights green chemistry benefits through aqueous medium, operational simplicity, and partial catalyst recyclability. Aligning seamlessly with global sustainability mandates, this work is closest to 'Responsible Consumption and Production,' SDG, offering a concrete advancement toward safer, eco-compatible chemical production practices.

Keywords: Heterocyclic Compound, DHPM, SNF, Bronsted Acid, Biginelli Reaction.

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INTRODUCTION

The synthesis of dihydropyrimidinones (DHPMs), first reported by Biginelli in 1893, involves an acid-catalysed three-component condensation of a β -keto ester, an aldehyde, and urea or thiourea.^{1,2} Despite its simplicity, the classical method suffers from limitations such as harsh conditions, extended reaction times, and moderate yields, particularly with substituted aldehydes, along with limited tolerance toward acid-sensitive functionalities.^{3,4} Multicomponent reactions (MCRs) have emerged as an efficient alternative, offering improved atom economy, reduced reaction steps, and enhanced sustainability.⁵ DHPMs, as pyrimidine-based heterocycles, are of significant interest due to their broad spectrum of biological activities, including antibacterial, antifungal, anti-inflammatory, antioxidant, and antitumor properties.⁶⁻¹³ They also serve as calcium channel modulators, antihypertensive agents, and inhibitors of DNA ligase I and HIV-1 replication.¹⁴⁻¹⁷ The therapeutic relevance of related heterocyclic systems is exemplified by drugs such as nifedipine, lercanidipine, and amlodipine,¹⁸⁻²⁰ while monastrol represents a notable DHPM derivative with promising anticancer activity through selective inhibition of kinesin-5 (Eg5).²¹⁻²³ Over the past decades, significant modifications of the classical Biginelli reaction have been developed to enhance the synthesis of DHPM derivatives. Alternative activation methods, including microwave-assisted²⁴ and L-proline-based organocatalysis²⁵, have improved reaction efficiency under milder conditions. Various Lewis acid catalysts such as $\text{Ce}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ ²⁶, $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ ²⁷, TiO_2 ²⁸, and $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$ ²⁹ have been employed to achieve higher yields with operational simplicity. Additionally, heteropoly acids and nanostructured heterogeneous systems have advanced catalyst recyclability and sustainability.³⁰⁻³⁴ Other catalysts like $p\text{-TsOH} \cdot \text{H}_2\text{O}$ ³⁵, H_3BO_3 ³⁶, and $\text{Fe}(\text{OTf})_3 \cdot 6\text{H}_2\text{O}$ ³⁷ have further expanded substrate scope and optimised reaction conditions. Despite significant advances in Biginelli reaction methodologies, many reported protocols still rely on corrosive acids, expensive or metal-based catalysts, hazardous organic solvents, and prolonged reaction times, limiting their sustainability and practical applicability.

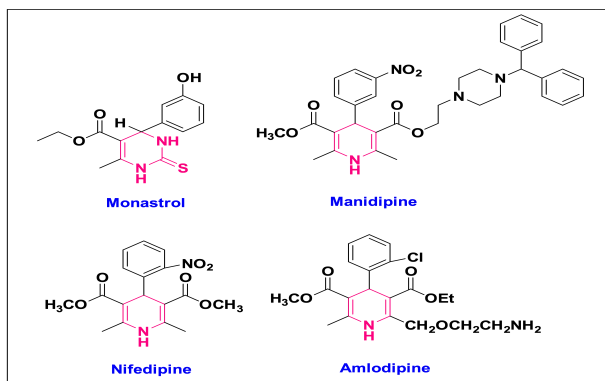


Fig.-1: Commercially Important Drugs Relevant to DHPM

Consequently, the development of environmentally benign, cost-effective, and efficient synthetic strategies remains highly desirable.³⁸⁻⁴⁰ Among green solvents, water has emerged as an ideal reaction medium due to its non-toxic, non-flammable, and sustainable nature. Moreover, the hydrophobic effect and hydrogen-bonding network of water can enhance substrate interactions, stabilize reactive intermediates, accelerate the condensation process, and suppress side reactions, leading to improved reaction efficiency and simplified product isolation. In this study, Sulfonated Naphthalene Formaldehyde (SNF) acts as a Brønsted acid catalyst, efficiently promoting the Biginelli reaction in water without hazardous solvents. The resulting DHPMs precipitate directly, enabling easy isolation by filtration while the catalyst remains in solution. This approach reduces solvent use, simplifies workup, and aligns with Green Chemistry principles. As part of our ongoing interest, we investigated the application of Sulfonated Naphthalene Formaldehyde (SNF) as a catalyst in the Biginelli reaction for the synthesis of Dihydropyrimidinones derivatives. The reactions were carried out in water as an environmentally friendly solvent, where the water-soluble SNF catalytic system facilitates effective interaction of the reactants and accelerates the reaction. The influence of key reaction parameters such as catalyst concentration, temperature, and reaction time was systematically examined to determine the optimum conditions. The developed protocol offers a simple, eco-friendly, and efficient approach for synthesising DHPM derivatives in good to excellent yields, consistent with the principles of Green Chemistry.

EXPERIMENTAL

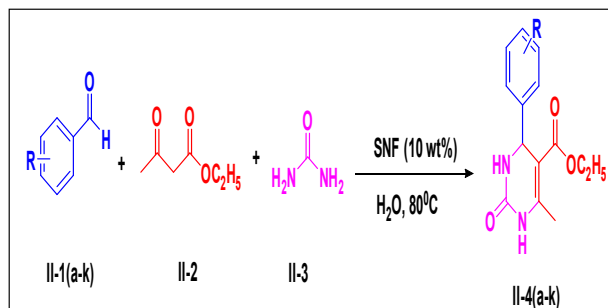
Material and Method

All chemicals and solvents employed for the synthesis of dihydropyrimidinone derivatives were of analytical grade and were obtained from commercial suppliers such as Sigma-Aldrich. The reagents were used as received unless further purification was required. The progress of the reactions was monitored by thin-layer chromatography (TLC) using silica gel plates. The melting points of the synthesised compounds were determined using the capillary tube method and are reported without correction. Structural elucidation and confirmation of the synthesised products were accomplished through infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy. The IR spectra were recorded on a PerkinElmer FT-IR spectrometer employing KBr pellets. The ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were obtained on a Bruker AVANCE III spectrometer using DMSO-d₆ as the solvent and tetramethylsilane (TMS) as the internal reference standard.

General Procedure for the Synthesis of DHPM

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.2 mmol), and Sulfonated Naphthalene Formaldehyde (SNF) (10 wt %) was heated in water (10 mL) at 80 °C with continuous stirring. The progress of the Biginelli reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature, resulting in the precipitation of the corresponding Dihydropyrimidinones derivative. The solid product was collected by simple filtration and washed with cold distilled water (2 × 5 mL) to remove residual catalyst and water-soluble impurities, followed by recrystallisation from ethanol to afford the pure compound. The synthesised products were confirmed by comparison of their physical data with reported literature values. The aqueous filtrate containing the

dissolved SNF catalyst was reused directly in subsequent reaction cycles by adding fresh reactants under identical conditions, demonstrating acceptable catalytic activity over multiple runs with gradual reduction in efficiency.



Scheme-1: Multicomponent SNF-Catalyzed Synthesis of DHPM

RESULT AND DISCUSSION

The model Biginelli-type condensation of benzaldehyde as a representative aromatic aldehyde, ethyl acetate, and urea was selected to optimise the reaction conditions for the synthesis of dihydropyrimidinone (DHPM) derivatives. The optimisation results are summarised in Table-1.

Table-1: Optimisation of Reaction Conditions for the Synthesis of Dihydropyrimidinone (DHPM)

Entry	Catalyst	Amount(wt%)	Solvent	Temp.(°C)	Time(hr)	Yield (%) ^x
1	-	-	-	60	24	4
2	-	-	-	80	12	12
3	-	-	-	80	12	22
4	SNF	2.5	-	80	8	33
5	SNF	5	-	80	6	45
6	SNF	7.5	-	80	5	54
7	SNF	10	-	80	3.5	67
8	SNF	12.5	-	80	3.5	69
9	SNF	15	-	80	3.5	69
10	SNF	10	DCM	80	2.5	72
11	SNF	10	Toluene	80	3	71
12	SNF	10	EtOH	80	2.5	76
13	SNF	10	H ₂ O	80	2	83

^x is the isolated yield of the product.

Control experiments without a catalyst showed negligible product formation even after prolonged heating, confirming that thermal activation alone is insufficient for the Biginelli reaction. The introduction of SNF significantly enhanced both reaction rate and yield, with 10 wt % identified as the optimal loading; higher amounts offered no additional benefit, indicating catalyst saturation. Solvent screening revealed that water is the most effective medium, providing higher yields in shorter reaction times compared to organic solvents due to efficient activation of benzaldehyde by SNF in aqueous conditions. Overall, the optimised catalytic system comprising 10 wt% SNF in water constitutes a simple, efficient, and environmentally sustainable protocol for the synthesis of dihydropyrimidinones (DHPMs). The methodology affords high product yields within shorter reaction times while eliminating the use of hazardous organic solvents, thereby enhancing operational efficiency and reducing environmental impact. These attributes underscore its practical utility and strong alignment with the fundamental principles of Green Chemistry. To further evaluate the catalytic efficiency of the developed protocol, a systematic comparison of various catalysts was conducted for the model Biginelli reaction using benzaldehyde as the representative aromatic aldehyde under identical reaction conditions (Table-2).

A comparative study of various catalysts for the model Biginelli reaction revealed that conventional Lewis acids such as ZnCl₂ and MgBr₂ provide only moderate yields with longer reaction times, likely due to limited efficiency in aqueous media. Brønsted acid catalysis with acetic acid improved both yield and rate, while other Lewis acids and neutral catalysts showed moderate to poor performance.

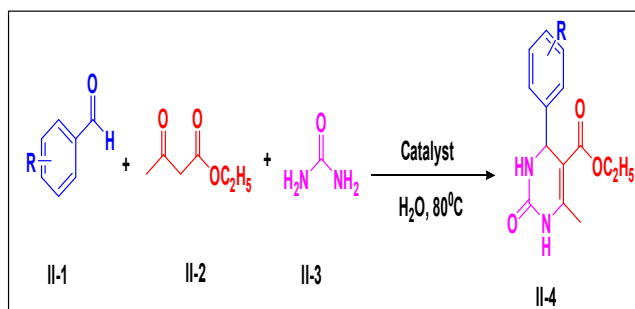


Table-2: Comparative Evaluation of Commercially Available Catalysts and SNF for the Synthesis of DHPM

Entry	Catalyst	Time(h.)	Conversion(%)	Yield(%) ^x
1	ZnCl ₂	5	84	63
2	MgBr ₂	4.5	88	73
3	CH ₃ COOH	3	93	78
4	SnCl ₄	4	84	69
5	Ph ₃ P	8	70	56
6	FeCl ₃	6	76	60
7	ZnO	3.5	88	71
8	P ₂ O ₅	3	90	75
9	SNF	2	100	83

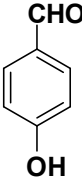
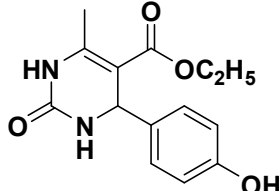
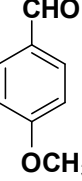
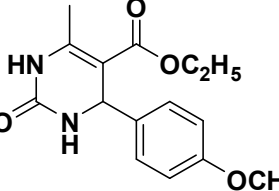
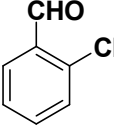
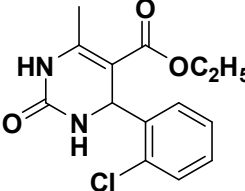
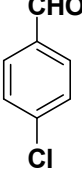
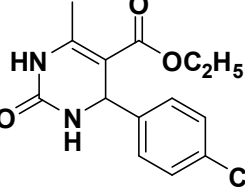
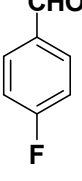
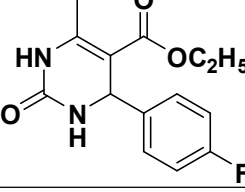
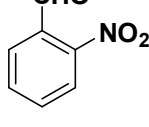
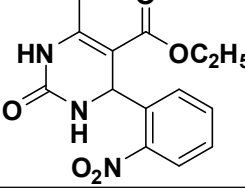
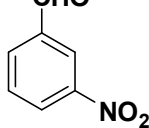
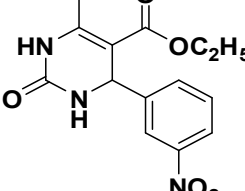
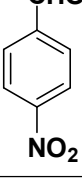
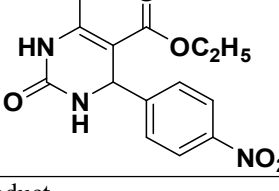
a) Catalyst loading was kept at 10 mol % (molecular catalysts) or 10 wt % (polymeric catalysts).

b) Reaction conditions: water is used as a solvent with reaction temp. Maintained at 80 °C.

Although P₂O₅ gave relatively better yield, its role is mainly as a dehydrating agent rather than an effective catalyst. In contrast, Sulfonated Naphthalene Formaldehyde (SNF) exhibited superior catalytic performance, achieving complete conversion and the highest product yield within the shortest reaction time under aqueous conditions. This enhanced efficiency is attributed to its strong Brønsted acidity and excellent water solubility, which promote effective reactant activation and accelerate the key steps of the reaction. Overall, SNF outperforms conventional catalysts by providing higher yields, faster reaction rates, and excellent compatibility with environmentally benign aqueous media, making it a promising catalyst for sustainable organic synthesis.

Table-3: Optimisation of Substrate Scope for the Synthesis of Dihydropyrimidinone under Optimised Conditions.

Entry	Aldehyde	Product	Time (h.)	Yield (%) ^x	M.P.	
					Obs.	Rep. ^[41-44]
4a			2	83	201-203	202
4b			2.5	81	190-192	192-194
4c			2.5	80	164-166	164-166

4d			3.5	73	227-229	228-229
4e			3	75	198-200	199-200
4f			2	84	212-214	213-215
4g			1.5	86		--
4h			1	91	184-185	182-184
4i			2	87	213-215	213-215
4j			1.5	92	233-235	233-234
4k			1	95	206-208	206-207

x is the isolated yield of the product.

Substrate scope investigations (Table-3) demonstrated the broad applicability and efficiency of the optimised reaction conditions (10 wt % SNF in water at 80 °C) for the synthesis of dihydropyrimidinones (DHPMs). The model reaction employing benzaldehyde afforded the corresponding DHPM in 83% yield within 2 h, establishing the effectiveness of the catalytic system. Aromatic aldehydes bearing electron-donating substituents generally furnished the desired products in moderate yields (73–81%) with relatively longer reaction times (2.5–3.5 h), reflecting the reduced electrophilicity of the carbonyl carbon and consequently slower reaction rates. In contrast, aldehydes containing electron-withdrawing substituents exhibited significantly enhanced reactivity, affording the corresponding DHPMs in excellent yields (84–95%) within shorter reaction times (1–2 h). The electron-deficient nature of these substrates facilitates nucleophilic attack by increasing the electrophilicity of the aldehydic carbon, thereby accelerating the key condensation and cyclisation steps of the Biginelli reaction. These findings clearly demonstrate that the electronic nature of the aldehyde substituents plays a decisive role in governing the reaction efficiency, with electron-withdrawing groups promoting superior catalytic performance under SNF-catalyzed aqueous conditions.

Spectroscopic Characterisation for Selected Compounds

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

IR (KBr, cm^{-1}): 1088, 1210, 1457, 1604, 1710, 2939, 3289, 3410; ^1H NMR (DMSO- d_6 , 300 MHz, δ ppm): 1.42(t, 3H), 2.61 (s, 3H), 4.20 (q, 2H), 5.14 (d, 1H), 5.63 (d, 1H), 7.18–7.36 (m, 5H), 8.52 (s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6 , δ ppm): 15.30, 19.58, 53.75, 69.29, 106.00, 125.34, 126.70, 127.90, 142.59, 143.66, 150.12, 160.62; MS (m/z): 261(M+)

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

IR (KBr, cm^{-1}): 1539, 1636, 1726, 3238; ^1H NMR (DMSO- d_6 , 300 MHz, δ ppm): 1.21 (t, 3H), 2.08 (s, 3H), 2.42 (s, 3H), 4.34 (q, 2H), 5.79 (d, 1H), 7.28 (d, 2H), 7.49 (d, 2H), 7.61 (s, 1H), 8.68 (s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6 , δ ppm): 15.12, 18.42, 56.01, 58.76, 61.14, 100.85, 118.32, 129.24, 137.96, 147.28, 161.02, 163.91, 182.86; MS (m/z): 274 (M+)

Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c)

IR (KBr, cm^{-1}): 1644, 1727, 3248, 3346, 3512; ^1H NMR (DMSO- d_6 , 300 MHz, δ ppm): 1.10 (t, 3H), 2.31 (s, 3H), 3.91 (q, 2H), 5.07 (s, 1H), 6.55 (d, 1H), 6.67 (d, 2H), 7.08 (t, 1H), 7.71 (s, 1H), 9.08 (s, 1H), 9.29 (s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6 , δ ppm): 14.9, 18.6, 54.0, 60.1, 100.4, 113.2, 115.1, 117.9, 130.3, 147.2, 148.9, 153.3, 158.4, 166.3; MS (m/z): 276 (M+)

Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)

IR (KBr, cm^{-1}): 1694, 1724, 2984, 3262, 3404; ^1H NMR (DMSO- d_6 , 300 MHz, δ ppm): 1.15 (t, 3H), 2.26 (s, 3H), 3.99 (q, 2H), 5.16 (s, 1H), 6.67 (d, 2H), 7.14 (d, 2H), 7.54 (s, 1H), 8.96 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6 , δ ppm): 15.28, 18.05, 53.21, 59.14, 100.18, 114.96, 127.62, 136.98, 147.68, 152.74, 156.63, 165.71; MS (m/z): 276 (M+).

CONCLUSION

An environmentally sustainable and effective protocol was established for the production of biologically important Dihydropyrimidinones via an SNF-catalyzed Biginelli reaction in aqueous medium. Under optimised conditions, aromatic aldehydes, ethyl acetoacetate, and urea afforded the corresponding DHPM derivatives in decent to outstanding yields (73–95%) within relatively short reaction times. From a sustainability perspective, this methodology successfully eliminates the need for hazardous, volatile organic solvents by utilising water as a clean reaction medium. Furthermore, the operational simplicity of the protocol is highlighted by the direct precipitation and easy isolation of the target products, leaving the active catalyst in the aqueous phase. The recovered catalyst can be directly recycled for up to five consecutive runs with acceptable retention of catalytic efficiency, thereby significantly minimising chemical waste generation. Ultimately, this research directly addresses a major challenge in modern synthetic chemistry by providing a metal-free, low-waste alternative to traditional, resource-intensive Biginelli methods. By seamlessly aligning with UN Sustainable Development Goal 12 (Responsible

Consumption and Production), this strategy offers a scalable, eco-compatible blueprint that bridges the gap between fundamental organic synthesis and practical, closed-loop industrial process engineering.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-12: Responsible Consumption and Production*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

S. S. Pawde  <https://orcid.org/0000-0001-6653-2307>

M. H. Gagare  <https://orcid.org/0009-0000-6686-3632>

S. S. Patil  <https://orcid.org/0000-0002-9661-6269>

D. B. Muley  <https://orcid.org/0000-0001-6653-2307>

A. S. Patki  <https://orcid.org/0009-0002-4444-8723>

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