Research Article

A NOVEL, EFFICIENT, GREEN METHODOLOGY FOR BIGINELLI-REACTION: BIODEGRADABLE SURFACTANT (RHAMNOLIPID)-CATALYZED SYNTHESIS OF DIHYDROPYRIMIDINES

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Article DOI:

10.55434/CBI.2024.10104

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Received- 05-05-2024
Accepted- 30-06-2024

ISSN 0799-3757

https://caribjscitech.com/

Abstract

The current study aims to establish a simple, green, and effective technique for synthesizing 4-aryl-1,2,3,4-tetrahydropyrimidine-2(1*H*)-ones/thione using a novel rhamnolipid catalyst (biosurfactant) in water as a solvent.

Keywords:

Rhamnolipid; biosurfactant; DHPMs; β-keto ester; aldehydes;urea/thiourea

Introduction

The one-pot acid cyclocondensation of an aldehyde, a β-keto ester, and urea or thiourea to create 3,4-dihydropyrimidin-2(1H)-ones/thiones is catalyzed by the Biginelli reaction, a conventional three-component reaction. Dihydropyrimidones (DHPMs) are well-known scaffolds having a range of pharmacological effects.[1-10] As the essential building blocks of various calcium channel blockers, antihypertensive, anticancer, α1-adrenergic antagonist, antimycobacterial, and anti-inflammatory capabilities, dihydropyrimidines have demonstrated noteworthy biological and pharmacological properties. Numerous alkaloids with DHPM moiety that were derived from marine sources shown significant biological activity.[11-18]

Apart from metal-organic frameworks, a number of techniques, including homogeneous and heterogeneous catalysts, have been reported for the synthesis of DHPM,[19-27] however, they are not without drawbacks, including lengthy reaction durations, the need for costly reagents and catalysts, low yields, toxic solvents, etc. Therefore, the primary emphasis of organic and medicinal chemists has been their synthesis. Over the past 20 years, we have also conducted a great deal of study in the area of Biginelli chemistry. In December 2002, we are the first authors in the literature to describe synthesizing Biginelli compounds (DHPMs) utilizing $Bi(OTf)_3$ at ambient temperature.[28] Afterwards, our research group provided a number of approaches associated with the title work.[29-34] Also known as surface-active agents of biological origin, biosurfactants have gained recognition in the industry for their unique capacity to be environmentally benign.[35-38] Since then, a large number of research teams from around the world have studied biosurfactants in great detail with some aspects still being unknown.

The five primary categories of biosurfactants used in the detergent, food, pharmaceutical, and agricultural sectors are phospholipids, glycolipids, and fatty acids; lipopeptides and lipoproteins; polymeric biosurfactants, and particle biosurfactants.[39-58] Data shows that over 250 patents have been issued thus far on these incredible biodegradable substances. It has also been observed that microbial biosurfactants have an advantage over plant-based surfactants due to their multifunctional properties, quick synthesis, and capacity for scaling up. A subgroup of glycolipids known as rhamnolipids is made up of mono- and disaccharides bonded to carboxylic acid via glyosidic bonds. These bio-surfactants are derived from Pseudomonas aeruginosa bacteria and are used as complexing, emulsifying, and foaming agents. Despite having a well-documented safety profile and potent surface activity, these ingredients have not yet been used in pharmaceutical formulations and are awaiting US FDA approval. This field has not received much attention from researchers and has only been examined by a small number of them.[59-62] The review of the literature revealed that rhamnolipid has not yet been identified as a catalyst for the traditional Biginelli reaction.

Water is cheap and harmless for the environment when compared to organic solvents. It can be used as reaction media to carry out organic reactions including Benzoin condensation, Diels-Alder, Claisen condensation, Aldol condensation, Mannich, and Michael addition reactions.[63-67] Surfactants have been employed as effective catalysts in a variety of chemical reactions, and their presence in water can solubilize organic materials or create colloidal dispersions that are very stable.

Therefore, there is an enormous need to develop a straightforward, affordable, and environmentally friendly way of synthesizing these scaffolds with higher yields and reaction speeds, taking in mind the endless need for Biginelli-scaffolds and green chemistry. Therefore, employing rhamnolipid as a possible catalyst and water as the solvent, a green approach for the one pot synthesis of Biginelli scaffolds by both microwave and traditional methods was developed.

Experimental Section

All the used chemicals were of analytical grade and purchased from Merck, Mumbai. The reactions were monitored by TLC on precoated silica gel 60 F254 and the spots were visualized in UV-light at 254 nm. Melting points were observed in open capillaries using Buchi melting point apparatus and are uncorrected. IR, ^{1}H NMR and Mass spectras were recorded on Perkin Elmer RX1-FTIR, JEOL 400 spectrometer using internal standard as TMS and JEOL DX 300 in E1 ionization method at 70ev respectively. The elemental analyses of the compounds were recorded using Perkin Elmer series 2400 analyzer.

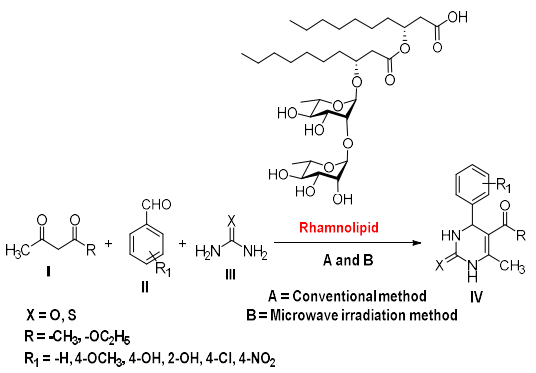
General Procedure for the synthesis of dihydropyrimidinones/thiones (IVa-IVl)

Conventional Method: The mixture of *β*-ketoester (0.01 mol, **I**), aldehyde (0.01 mol, **II**), urea/ thiourea (0.015 mol, **III**) and rhamnolipid (10% *w/v* in water) was reflux heated for 4-5 hrs with magnetic stirrer. The completion of the reaction was observed by TLC using ethylacetate: hexane (6:4) as the mobile phase. The reaction mixture after adjusting to room temperature was poured into 100 mL of cold water and stirred for 5 min. The separated solid in the mixture was filtered under suction, washed with cold water and then recrystallized from ethanol to recover the pure product **(IV)**.

Microwave Irradiation Method: The mixture of *β*-ketoester (0.01mol, **I**), aldehyde (0.01 mol, **II**), urea or thiourea (0.015 mol, **III**) and rhamnolipid (10% *w/v* in water) was subjected to microwave irradiation at 220 volt for 5-6 min. The completion of the reaction was observed by TLC using ethylacetate: hexane (6:4) as the mobile phase. The reaction mixture after adjusting to room temperature was poured into 100 mL of cold water and stirred for 5 min. The separated solid in the mixture was filtered under suction, washed with cold water and then recrystallized from ethanol to recover the pure product **(IV)**.

Results and Discussion

The 4-(substituted phenyl-)-1,2,3,4-tetrahydropyrimidine-2-(1*H*)-ones/thiones (**IVa-IVl**) were prepared by one pot Biginelli reaction using water as solvent and rhamnolipid as a catalyst as represented in Scheme 1.



Scheme 1: Rhamnolipd-catalyzed Biginell reaction

The generated compounds were purified using liquid column chromatography. All reactions were observed using TLC, and the derivatives were supported by IR, Mass, and ^{1}H NMR spectral data and compared with the existing literature.[25] The IR spectra of compound **IVa** revealed absorption bands at 3306, 3172, and 1702 cm^{-1}, indicating the presence of -NH, Ar-H, and C=O groups, respectively. The base peak of mass spectra is denoted as M+1 and is also shared by all of the following derivatives. The ^{1}H NMR spectrum exhibits signals at δ 2.2 (s, -$COCH_3$), 7.2 (m, Ar-H), 7.8 and 9.1 (br, -NH). **Table 1** shows the physical properties of the produced compounds.

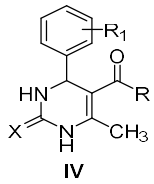
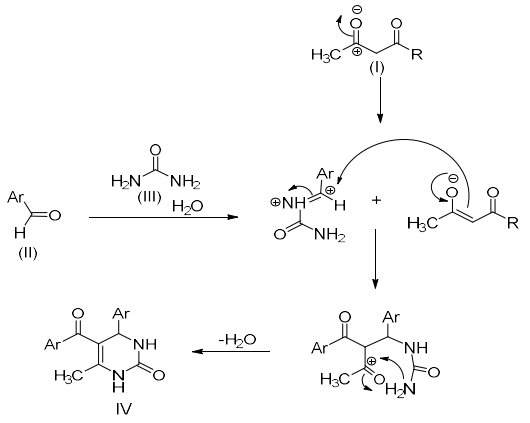


Table 1: Physical data of the synthesized DHPM derivatives (***IV*a-*IV*l**)

S. No.	Compound Code	R1	R	X	% Yield		M.P (°C)	
					Conventional Method[a]	Microwave Method[a]	Found (°C)	Reported (°C)
1	***IV*a**	C_6H_5	CH_3	O	92	95	229-232	233-235
2	***IV*b**	C_6H_5	OC_2H_5	O	90	96	203-205	201-202
3	***IV*c**	4-$OCH_3C_6H_4$	OC_2H_5	O	87	89	199-201	200-201
4	***IV*d**	4-OHC_6H_4	OC_2H_5	O	89	92	226-229	222-229
5	***IV*e**	2-OH-C_6H_4	OC_2H_5	O	90	94	199-201	201-202
6	***IV*f**	4-ClC_6H_4	OC_2H_5	O	91	95	209-211	212-214
7	***IV*g**	4-$NO_2C_6H_4$	OC_2H_5	O	90	93	206-208	207-209
8	***IV*h**	C_6H_5	OC_2H_5	S	92	96	208-210	204-206
9	***IV*i**	C_6H_5	CH_3	S	91	95	216-218	219-220
10	***IV*j**	4-(OCH_3)-C_6H_4	CH_3	O	92	96	165-168	167-169
11	***IV*k**	4-ClC_6H_4	OC_2H_5	S	92	95	190-192	192-194
12	***IV*l**	4-OHC_6H_4	OC_2H_5	S	86	88	217-219	216-218

[a]Yields refer to pure isolated products

The Biginelli reaction mechanism is illustrated in **Scheme 2**. It entails the *micellar catalysis of the biosurfactant rhamnolopid* to generate an intermediate *N*-acyliminium ion from the aldehyde and urea components. An open chain ureide is created when the *β*-ketoester intercepts the iminium ion, potentially *via* its enol tautomer. This ureide then undergoes cyclization and dehydration to form dihydropyrimidinones (**IV**).



Scheme 2: Proposed mechanism of rhamnolipid catalyzed Biginelli reaction.

Conclusion

A highly simple procedure been reported for the synthesis of dihydropyrimidine derivatives. The reaction is catalyzed by rhamnolipid (biosurfactant) in aqueous media under two experimental methods. This method has many advantages like inexpensive, less toxic, high yield and eco-friendly. The yield of the synthesized compound was found to be more under MW-irradiation method than conventional method. These studies can be used for designing novel synthetic routes for the preparation of pyrimidine scaffold.

Acknowledgements

The author Dr.D.P. Beda wish to express their sincere thanks to the Management and Principal of GITAM School of Pharmacy, Hyderabad, Telangana, India, for providing suitable research facilities for carrying out the work.

Conflict of interest

All authors declare that they have no conflict of interest.

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