chemistry proceedings

MDPI

Proceeding Paper

An Efficient Synthesis and Antibacterial Activity of Some Novel 3,4–Dihydropyrimidin-2-(*1H*)-Ones †

Nilesh S. Pawar [1,*], Pramod N. Patil [2] and Rajashri N. Pachpande [3]

[1] Department of Chemistry, Pratap College, Amalner 425401, India
[2] Department of Applied Science and Humanities, R. C. Patel Institute of Technology, Shirpur 425405, India; pramodpatil1630@gmail.com
[3] Senior College, DNCVPS Shirish Madhukarrao Chaudhari College, Jalgaon 425001, India; rajashrinp10@gmail.com
* Correspondence: nileshpawar1329@rediffmail.com
† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

Abstract: We have efficiently synthesized mono as well as bis and spiro cyclic products of 3,4-dihydropyrimidin-2(*1H*)-ones (DHPMs) by refluxing a reaction mixture of the three components in deep eutectic solvent (*DES*) to generating "libraries from libraries". Synthesized Spiro fused heterotricyclic compounds containing urea moiety are potent against bacteria. Overall, in the antibacterial study, from the synthesized compounds, some of the 3,4–dihydropyrimidin-2-(*1H*)-one compounds were found to possess anti-bacterial efficacy.

Keywords: 3,4-dihydropyrimidin-2(*1H*)-ones; bis-dihydropyrimidinones; spirofused heterotricyclic; deep eutectic solvent and antibacterial activity

check for updates

Citation: Pawar, N.S.; Patil, P.N.; Pachpande, R.N. An Efficient Synthesis and Antibacterial Activity of Some Novel 3,4–Dihydropyrimidin-2-(*1H*)-Ones. *Chem. Proc.* **2021**, *8*, 37. https://doi.org/10.3390/ecsoc-25-11720

Academic Editor: Julio A. Seijas

Published: 14 November 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

A tremendous increase in activity has occurred, as evidenced by the growing number of publications and patents on the subject of Biginelli reaction, i.e., 3,4-dihydropyrimidin-2-(*1H*)-one. This is mainly due to the fact that the multi-functionalized dihydropyrimidine scaffold (DHPMs, "Biginelli compounds") represents a heterocyclic system of remarkable pharmacological efficiency. In recent decades, a broad range of biological effects, including antiviral, antitumor, antibacterial, and anti-inflammatory activities, has been ascribed to these partly reduced pyrimidine derivatives [1]. More recently, appropriately functionalized DHPMs have emerged as, e.g., orally active antihypertensive agents (1, 2, 5) (Figure 1) [2–4] or α_{1a} adrenoceptor-selective antagonists (**3**) (Figure 1) [5,6]. A very recent highlight in this context has been the identification of the structurally rather simple DHPM Monastrol (**4**) (Figure 1) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and, therefore, causes cell cycle arrest [7,8]. Monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs [7,8]. Furthermore, apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated [9]. Most notable among these are the batzelladine alkaloids A and B (e.g., **5**), which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy [10].

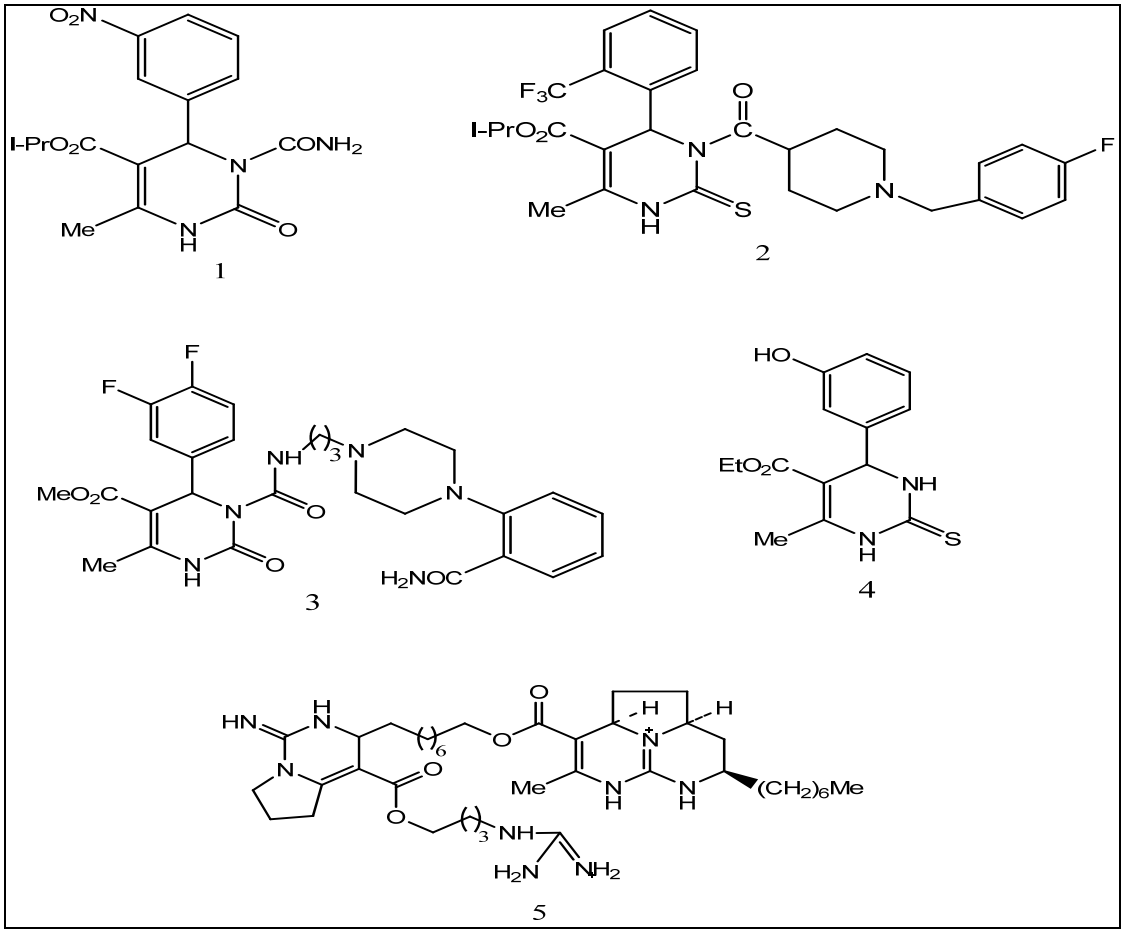


Figure 1. Reported derivatives of 3,4–dihydropyrimidin-2-(*1H*)-Ones.

Currently, there is a great variety of suitable reaction conditions for Biginelli condensations have been reported including classical conditions with microwave irradiation and by using Lewis acids, as well as protic acids, as promoters. Promoters such as conc. HCl [11], BF_3•OEt_2 [12], PPE [11], KSF clay [13], $InCl_3$ [14], $LaCl_3$ [15–17], lanthanide triflate [18], H_2SO_4 [15–17], ceric ammonium nitrate (CAN) [19], $Mn(Oac)_3$ [20] ion-exchange resin [21], 1-n-butyl-3-methyl imidazolium tetrafluoroborate ($BMImBF_4$) [22], $BiCl_3$ [23], $LiClO_4$ [24], $InBr_3$ [25], $FeCl_3$ [26], $ZrCl_4$ [27], $Cu(Otf)_2$ [28], $Bi(Otf)_3$ [29], LiBr [30], ytterbium triflates [31], NH_4Cl [32–34], $CdC1_2$ [35], TMSCl [36], $RuCl_3$ [37], NBS [38], etc., have been found to be effective and these methods tack the simplicity of the original one-pot Biginelli protocol.

However, some of these methods require the use of toxic reagents in combination with Bronsted acids, such as hydrochloric acid and acetic acid, as additives. Many of these methods involve expensive reagents, stoichiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields, and incompatibility with other functional group.

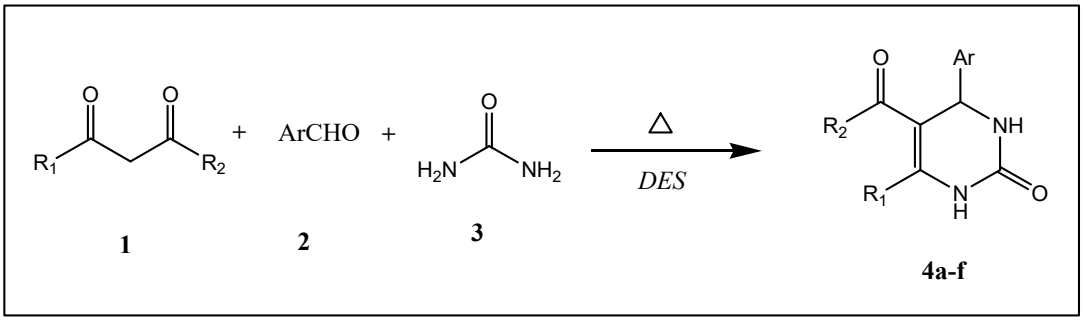
The synthesis of DHPMs is thus of significant importance in organic synthesis due to their wide range of biological activities. In view of our interest to develop greener protocols for organic transformations, we herein report the application of *DES* (K_2CO_3 + Glycerol, 1:5) as catalysts as solvent for synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones using a multicomponent condensation approach. Additionally, a large and exciting extension of 3,4-dihydropyrimidin-2(*1H*)-ones (DHPMs) to new reaction utilizing parallel organic synthesis arrays, as demonstrated by the use of easily and cheaply available *DES* (K_2CO_3 + Glycerol, 1:5), the potential of the spirocyclic products for generating "libraries from libraries".

2. Results and Discussion

DES (K_2CO_3+Glycerol), ethyl acetoacetate, acetyl acetone, cyclohexanone, urea, thiourea, and aromatic aldehydes (Benzaldehyde, Vanillin, Cinnamaldehyde and Terphthaldehyde) obtain from s.d. Fine Chemical Ltd., Mumbai, India. Melting points were determined using open capillary method in the paraffin liquid and are uncorrected. IR spectra were recorded on a Perkin Elmer FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. The FAB mass spectra were recorded on a Jeol SX 102/Da-600 mass spectrometer. Reactions were monitored by TLC using $CHCl_3$:EtOH, (9:1) solvent system. All the products were characterized by comparing their IR, ^{1}H NMR, MS, and melting points with those reported in the literature.

2.1. General Procedure for Synthesis of Dihydropyrimidinones

A solution of an appropriate ethyl acetoacetate/acetyl acetone (1.2 mmol), corresponding aldehyde (1.0 mmol), urea (1.2 mmol), and *DES* (K_2CO_3+Glycerol) (20 mL) was heated under reflux for several hours (completion of reaction was monitored by TLC). The reaction mixture was washed thoroughly with water, filtered, and recrystallized from methanol to afford pure product. (Scheme 1 and Table 1).



Scheme 1. Synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones.

Table 1. Synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones.

Entry *	R1	R2	Ar	Products	Reaction Time (h)	Yield # (%)	m.p. (°C)
1	CH_3	OC_2H_5	C_6H_5-	4a	2	81	204–205
2	CH_3	CH_3	C_6H_5-CH = CH-	4b	1.5	80	171–173
3	CH_3	OC_2H_5	C_6H_5-CH = CH-	4c	1.5	76	231–232
4	CH_3	CH_3	*p*-OH,*m*-OCH_3 C_6H_5-	4d	3	75	210–213
5	CH_3	OC_2H_5	*p*-OH,*m*-OCH_3 C_6H_5-	4e	3	81	233–235
6	CH_3	OC_2H_5	-C_6H_5CHO	4f	5	70	> 300

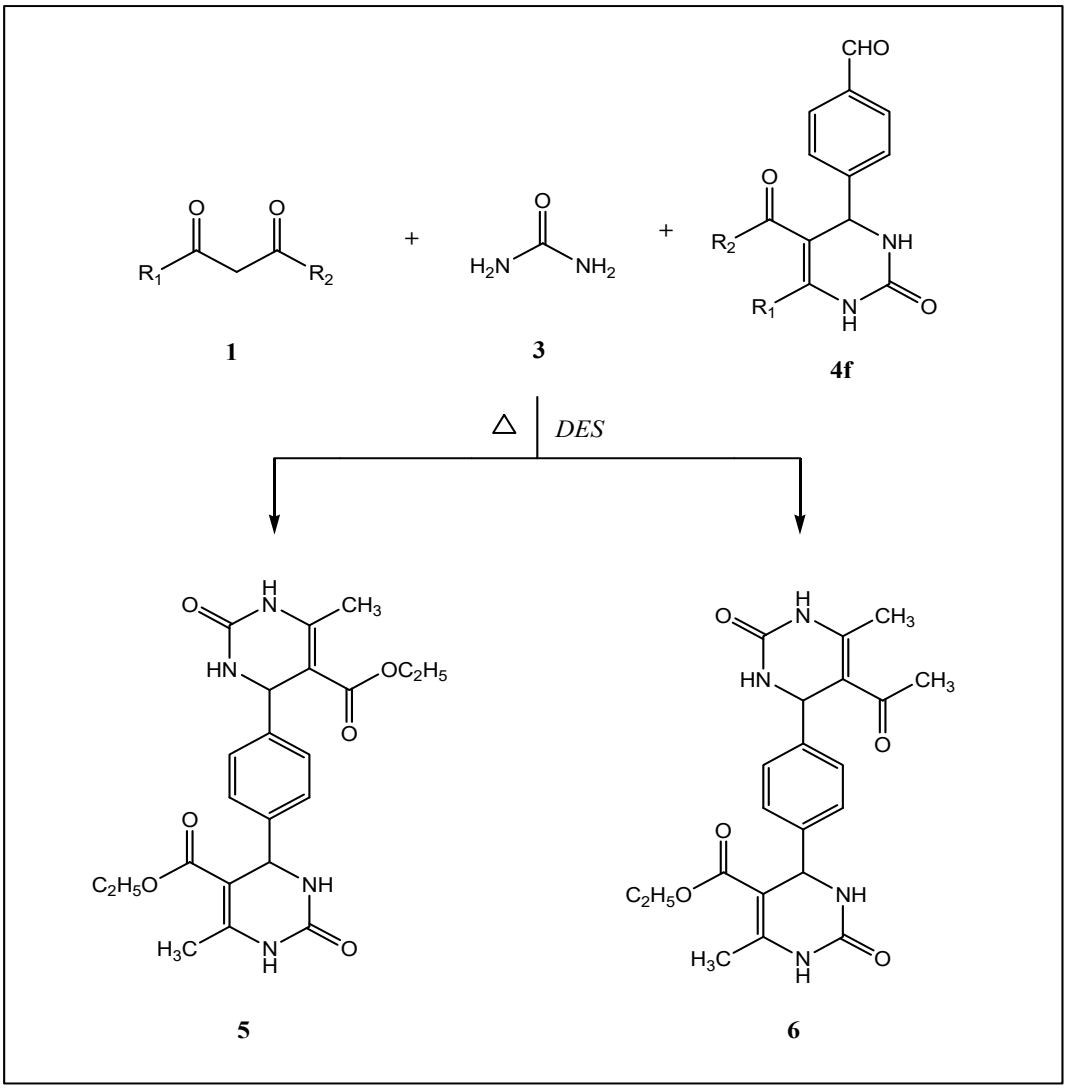
* All product were identified using comparison of their physical and spectral data (IR and NMR) with those reported in the literature [1,2,5,6,39–41] # Isolated yields. The spectral data of the some of the compounds are given below: Entries 2 and 4 (4b and 4d), the spectroscopic data is full agreement with the literature data. IR data: Frequency (cm^{-1}): Entry 1: (4a) 3238, 3117, 2980, 1722, 1697, 1644, 1462, 1419, 1383, 1367, 1340, 1313, 1289, 1272, 1217, 1180, 1087, 1027, 956, 879, 824, 756, 697, 661. Entry 3: (4e) 3335, 3342, 3098, 2978, 1689, 1642, 1492, 1373, 1121, 785. Entry 6: (4f) 2924, 2854, 1699, 1646, 1446, 1405, 1377, 1331, 1232, 722. ^{1}H NMR data (DMSO-d_6): Entry 1: (4a) δ = 9.18 (s, 1H, NH), 7.74 (s, 1H, NH), 7.22 (m, 5Harom), 5.14 (d, 1H, J = 3.6 H_2, H-4), 3.40 (q, 2H, J = 6.9 H_2, OCH_2), 2.24 (s, 3H, CH_3), 1.09 (t, 3H, J = 6.9 H_2, CH_3). Entry 3: (4c) δ = 1.06 (t, 3H, J = 7.0 H_Z), 2.50 (s, 3H), 3.95 (q,2H, J = 7.0 H_2), 4.24 (d, 1H, J = 6.0 H_2), 6.05 (dd, 1H, J = 16.4 H_Z), 6.2 (d, 1H, J = 16.4 H_Z), 7.25 (m, 5H) 7.45 (d, NH, J = 1.7 HZ), 8.95 (br, S, NH), Entry 5: (4e) δ = 1.093 (t, 3H, CH_3-CH_2), 2.245 (S, 3H, CH_3-C) 3.272 (s, 3H, CH_3-O), 3.989 (q, 2H, -CH_2), 5.073 (S, 1H, -OH), 6.722 (m, 3H, Ar-H), 7.623 (S, NH), 8.891 (S, NH). Entry 6: (4f) δ = 1.058 (t, 3H, CH_3-CH_2O), 1.199 (S, 3H, CH_3-C), 3.943 (q, 2H, -CH_2-O), 5.111 (S, 1H, OH), 7.160–7.869 (m, 4H, Ar-H), 9.076 (S, NH), 9.933 (S, 1H, CHO-). MS data: Entry 1 (4a): (ES/MS): *m*/*z* 259 (M-H), Entry 3 (4c): (EIMS): *m*/*z* 286 (M^+) 252, 224, 196, 149, 84.

2.2. Synthesis of Bis-Dihydropyrimidinones

Terphthaldehyde is an interesting class of bis aldehyde compounds which have two active site at which reaction is take place, i.e., two-CHO groups. The literature survey indicates that a limited amount of work has been performed on terphthaldehyde so that we have completed work on both active sites of terphthaldehyde.

2.3. General Procedure for Synthesis of Bis-Dihydropyrimidiones

The mixture of an aldehyde (1.0 mmol) urea (1.2 mmol), ethyl acetoacetate/acetylacetone (1.2 mmol) and *DES* (K_2CO_3+Glycerol) (25 mL) was heated under reflux on water bath for 4~5 h. The completion of reaction was monitored by TLC further the reaction mixture was cooled and poured on crushed ice. The solid was separated out and then filtered, washed with pet. ether, dried, and recrystallized using ethanol (Scheme 2 and Table 2).



Scheme 2. Synthesis of bis-3,4-dihydropyrimidin-2(*1H*)-one.

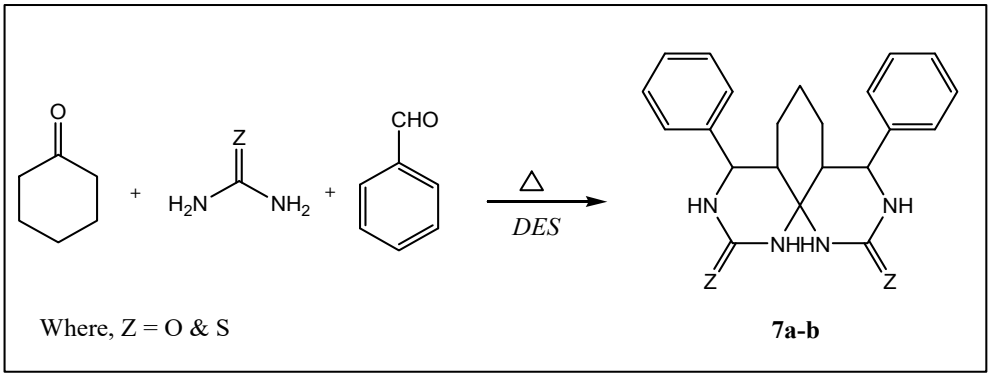
Table 2. Synthesis of bis-3,4-dihydropyrimidin-2(*1H*)-one.

Entry *	R_1	R_2	Products	Reaction Time (h)	Yield # (%)	m.p. (°C)
7	CH_3	OC_2H_5	5	5	75	>300
8	CH_3	CH_3	6	4	65	>300

* All product were identified using comparison of their physical and spectral data (IR and NMR) with those reported in the literature; # Isolated yields. The spectral data are given below: IR data: Frequency (cm^{-1}): Entry 8 (6): 2924, 2854, 1699, 1655, 1459, 1406, 1377, 1331, 1230, 1087, 801. ^{1}H NMR data (DMSO-d_6): Entry 7 (5): 1.075 (t, 3H, CH_3-CH_2O), 2.213 (s, 3H, CH_3-C), 3.945–3.961 (q, 2H, -CH_2-O), 5.114 (s,. 1H, -CH), 7.161–7.869 (m, 4H, Ar-H), 9.075 (s, NH), Entry 8 (6): 1.058 (t, 3H, CH_3-CH_2O), 1.139 (s, 3H, CH_3-C), 2.214 (s, 3H, CH_3-CO-), 3.945-3.962 (q, 2H, -CH_2-O), 5.114 (s, 1H, -CH), 7.160–7.870 (m, 4H, Ar-H), 9.074 (s, NH) MS data: Entry 7 (5): (ES/MS): *m*/*z* 441 (M-H), 441, 397, 259, 183, 89.

2.4. Synthesis of Spirofused Heterotricyclic Compounds

To a mixture of cyclohexanone (2.1 mL, 5.0 mmol), benzaldehyde (4.6 mL, 10.0 mmol), urea (4.1 gm, 15.0 mmol) or thiourea (4.6 gm, 15.0 mmol) and *DES* (K_2CO_3+Glycerol) (25 mL) with stirring. The resulting mixture was refluxed for 6 h. After completion of reaction as monitored by TLC using $CHCl_3$:EtOH, (8:2) solvent system, then reaction mixtures was cooled and pour into crushed ice and filtered. The crude residue was washed with pet. ether and then recrystallized with alcohol to afford the desired spiro fused heterotricyclic compound. (Scheme 3 and Table 3).



Scheme 3. Spirofused heterotricyclic compounds.

Table 3. Synthesis of Spiro fused heterotricyclic compounds.

Entry *	Z	Products	Reaction Time (hrs)	Yield # (%)	m.p. (°C)
9	O	7a	6	75	328
10	S	7b	6	78	>360

*All products were identified using comparison of their physical and spectral data (IR and NMR) with those reported in the literature. # Isolated yields. The spectral data given below: MS data: Entry 10 (7b): (EIMS): *m*/*z* 409 (M^+) 409, 333, 245, 154, 91.

Antibacterial Activity

Bioassay is important and crucial method in evaluation of bio-activity of the compounds and helpful to establish structure–activity relationship (SAR). In present work, all the synthesized compounds have been tested for their anti-bacterial potency against different bacterial species.

The bacterial potency is proportional to the diameter (in mm) of the zone of inhibition. The experiments were performed in duplicate and the average of the measured zones of inhibitions was considered and the results were summarized in Tables 4 and 5.

Table 4. Antibacterial activity data of 3,4-dihydropyrimidin-2-(*1H*)–one.

Entry	Compounds	Zones of Inhibition in mm at Concentration of 20 μg/mL			
		E. coli	*P. vulgaris*	*S. aureus*	*B. subtilis*
1	4a	—	—	—	—
2	4b	—	—	—	—
3	4c	—	—	—	—
4	4d	—	—	—	—
5	4e	—	03	—	03
6	4f	—	—	01	—
7	5	—	—	04	—
8	6	—	—	—	—

Table 5. Antibacterial activity data of spiro fused heterotricyclic compounds.

Entry	Compounds	Zones of Inhibition in mm at Concentration of 20 μg/mL			
		B. subtilis	*S. aureus*	*P. vulgaris*	*P. acurginosa*
9	7a	07	9	15	06
10	7b	17	15	19	09

In overall antibacterial study, from the synthesized compounds **4a–f, 5,** and **6,** some of 3,4–dihydropyrimidin-2-(*1H*)-one compounds were found to possess anti bacterial efficacy. No trend was observed between structural modification and antibacterial action to postulate any hypothesis. Among all synthesized compounds, **4e** may be due to *p*-OH and *m*-OCH_3 containing groups of benzene ring and **4f** and **5** these may be due to—CHO group possesses in benzene ring, exhibited remarkable antibacterial efficacy.

Although, in the case of synthesized spirofused heterotricyclic compounds (**7a,b**), compound **7a** containing urea moiety is potent against bacteria but compound **7b,** containing thiourea moiety, is more potent than all four tested bacterial species compared to compound **7a**.

3. Conclusions

In the present investigation, a reaction mixture consisting of aryl or aliphatic aldehydes, urea and ethyl acetoacetate, or acetyl acetone in presence of *DES* at heating condition only (Tables 1 and 2), because, first of all, we observe these reactions at room temperature but it does not obtain target products. After completion of reaction, the homogeneous mixture pour in cold water and tend to the isolation of pure mono, as well as bis 3,4-dihydropyrimidin-2(*1H*)-one in good yield. The amount of *DES* (K_2CO_3+Glycerol) molar ratio 1:5, we have been fixed on the basis of up to the obtained well homogeneity of all the three-components.

The classical Biginelli reaction is considerably extended use of cycloalkanones instead of 1,3-dicarbonyl compounds. The versatility of the method was then checked by using thiourea and urea to prepare spiro fused heterotricyclic compound (Table 3). Both these variation did not affect appreciably as the yield, as well as ease of workup procedure, only it needs more purification.

In presence of *DES* (K_2CO_3+Glycerol), the Biginelli reaction satisfactory fulfills the entire above requirement. Here, we use *DES* as one that is both cheap and a reagent with high shelf availability. *DES* are soluble in water and easily removed by simple workup procedure and it can be reuse up to three to four times well.

Author Contributions: Conceptualization, methodology by N.S.P. and he is guide in this research paper, writing—original draft preparation by co-author P.N.P. and R.N.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: No studies on human and animals.

Informed Consent Statement: No studies on human.

Data Availability Statement: All available details of data like M.P. IR, NMR, Mass mentioned in above paper.

Acknowledgments: Authors are very thankful to Principal J. S. Rane, Pratap College, Amalner for providing necessary laboratory facilities and also to SAIF, CDRI, Lucknow, INDIA, for providing a necessary valuable data of all the synthesized compounds.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Kappe, C.O. 100 years of the biginelli dihydropyrimidine synthesis. *Tetrahedron* **1993**, *49*, 6937–6963. [CrossRef]
2. Atwal, K.S.; Swanson, B.N.; Unger, S.E.; Floyd, D.M.; Moreland, S.; Hedberg, A.; O'Reilly, B.C. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro- 6- methyl-5-pyrimidinecarboxylic Acid Esters as Orally Effective, Antihypertensive Agents. *J. Med. Chem.* **1991**, *34*, 806–811. [CrossRef]
3. Rovnyak, G.C.; Atwal, K.S.; Hedberg, A.; Kimball, S.D.; Moreland, S.; Gougoutas, J.Z.; O'Reilly, B.C.; Schwartz, J.; Malley, M.F. Dihydropyrimidine calcium channel blockers. 4. Basic 3-substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents. *J. Med. Chem.* **1992**, *35*, 3254–3263. [CrossRef]
4. Grover, G.J.; Dzwonczyk, S.; McMullen, D.M.; Normandin, D.E.; Parham, C.S.; Sleph, P.G.; Moreland, S. Pharmacologic Profile of the Dihydropyrimidine Calcium Channel Blockers SQ 32,547 and SQ 32,946. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289–294. [CrossRef]
5. Nagarathnam, D.; Miao, S.W.; Lagu, B.; Chiu, G.; Fang, J.; Dhar, T.G.M.; Zhang, J.; Tyagarajan, S.; Marzabadi, M.R.; Zhang, F.Q.; et al. Design and Synthesis of Novel R1a Adrenoceptor- Selective Antagonists. Structure-Activity Relationship in Dihydropyrimidones. *J. Med. Chem.* **1999**, *42*, 4764–4777. [CrossRef]
6. Barrow, J.C.; Nantermet, P.G.; Selnick, H.G.; Glass, K.L.; Rittle, K.E.; Gilbert, K.F.; Steele, T.G.; Homnick, C.F.; Freidinger, R.M.; Ransom, R.W.; et al. In Vitro and in Vivo Evaluation of Dihydropyrimidinone C-5 Amides as Potent and Selective R1a Receptor Antagonists for the Treatment of Benign Prostatic Hyperplasia. *J. Med. Chem.* **2000**, *43*, 2703–2718. [CrossRef]
7. Mayer, T.U.; Kapoor, T.M.; Haggarty, S.J.; King, R.W.; Schreiber, S.L.; Mitchison, T.J. Small-Molecule Inhibitor of Mitotic Spindle Bipolarity Indentified in a Phenotype-Based Screen. *Science* **1999**, *286*, 971–974. [CrossRef]
8. Haggarty, S.J.; Mayer, T.U.; Miyamoto, D.T.; Fathi, R.; King, R.W.; Mitchison, T.J.; Schreiber, S.L. Dissecting Cellular Processes Using Small Molecules: Identification of Colchicine- Like, Taxol-Like and other Small Molecules that Perturb Mitosis. *Chem. Biol.* **2000**, *7*, 275–286. [CrossRef]
9. Heys, L.; Moore, C.G.; Murphy, P.J. The Guanidine Metabolites of Ptilocaulis Spiculifer and Related Compounds; Isolation and Synthesis. *Chem. Soc. Rev.* **2000**, *29*, 57–67. [CrossRef]
10. Patil, A.D.; Kumar, N.V.; Kokke, W.C.; Bean, M.F.; Freyer, A.J.; De Brosse, C.; Mai, S.; Truneh, A.; Carte, B. Novel Alkaloids from the Sponge Batzella sp.: Inhibitors of HIV gp120-Human CD4 Binding. *J. Org. Chem.* **1995**, *60*, 1182–1188. [CrossRef]
11. Kappe, C.O.; Falsone, S.F. Polyphosphate Ester-Mediated Synthesis of Dihydropyrimidines. Improved Conditions for the Biginelli Reaction. *Synlett* **1998**, *71*, 718–720. [CrossRef]
12. Hu, E.H.; Sidler, A.D.R.; Dolling, U.-H. Unprecedented Catalytic Three Component One-Pot Condensation Reaction: An Efficient Synthesis of 5-Alkoxycarbonyl- 4-aryl-3,4-dihydropyrimidin-2(*1H*)-ones. *J. Org. Chem.* **1998**, *63*, 3454–3457. [CrossRef]
13. Kappe, C.O.; Kumar, D.; Varma, R.S. Microwave-Assisted High- Speed Parallel Synthesis of 4-Aryl-3,4-dihydropyrimidin-2(*1H*)-ones using a Solventless Biginelli Condensation Protocol. *Synthesis* **1999**, 1799–1803. [CrossRef]
14. Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. A Revision of the Biginelli Reaction Under Solid Acid Catalysis. Solvent-free Synthesis of Dihydropyrimidines over Montmorillonite KSF. *Tetrahedron Lett.* **1999**, *40*, 3465–3468. [CrossRef]
15. Lu, J.; Ma, H. Iron(III)-Catalyzed Synthesis of Dihydropyrimidinones. Improved Conditions for the Biginelli Reaction. *Synlett* **2000**, 63–64. [CrossRef]
16. Ma, Y.; Qian, C.; Wang, L.; Yang, M. Lanthanide Triflate Catalyzed Biginelli Reaction. One-Pot Synthesis of Dihydropyrimidones under Solvent-Free Conditions. *J. Org. Chem.* **2000**, *65*, 3864–3868. [CrossRef]
17. Ranu, B.C.; Hajra, A.; Jana, U. Indium(III) Chloride-Catalyzed One-Pot Synthesis of Dihydropyrimidinones by a Three-Component Coupling of 1,3- Dicarbonyl Compounds, Aldehydes, and Urea: An Improved Procedure for the Biginell Reaction. *J. Org. Chem.* **2000**, *65*, 6270–6272. [CrossRef]

18. Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. One-pot synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones using lanthanum chloride as a catalyst. *Tetrahedron Lett.* **2000**, *41*, 9075. [CrossRef]
19. Bussolari, J.C.; McDonnell, P.A.J. Bismuth (III) nitrate catalyzed one-pot synthesis of 3,4-dihydro-pyrimidin-2-(*1H*)-ones: An improved protocol for the Biginelli reaction. *Org. Chem.* **2000**, *65*, 6777. [CrossRef]
20. Yadav, J.S.; Reddy, B.V.S.; Reddy, K.B.; Raj, K.S.; Prasad, A.R. Ultrasound-accelerated synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones with ceric ammonium nitrate. *J. Chem. Soc.* **2001**, 1939–1941.
21. Kumar, K.A.; Kasthuraiah, M.; Reddy, C.S.; Reddy, C.D. Mn (OAc) 3·2H2O-mediated three-component, one-pot, condensation reaction: An efficient synthesis of 4-aryl-substituted 3, 4-dihydropyrimidin-2-ones. *Tetrahedron Lett.* **2004**, *42*, 7873. [CrossRef]
22. Dondoni, A.; Massi, A. Parallel synthesis of dihydropyrimidinones using Yb(III)-resin and polymer-supported scavengers under solvent-free conditions. A green chemistry approach to the Biginelli reaction. *Tetrahedron Lett.* **2001**, *42*, 7975. [CrossRef]
23. Peng, J.; Deng, Y. Ionic liquids catalyzed Biginelli reaction under solvent-free conditions. *Tetrahedron Lett.* **2001**, *42*, 917. [CrossRef]
24. Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T.N.B. Bismuth(III)-Catalyzed Synthesis of Dihydropyrimidinones: Improved Protocol Conditions for the Biginelli Reaction. *Synlett* **2001**, *6*, 863. [CrossRef]
25. Yadav, J.S.; Subba Reddy, B.V.; Srinivas, R.; Venugopal, C.; Ramalingam, T. LiClO4-Catalyzed One-Pot Synthesis of Dihydropyrimidinones: An Improved Protocol for Biginelli Reaction. *Synthesis* **2001**, *9*, 1341. [CrossRef]
26. Fu, N.Y.; Yuan, Y.F.; Cao, Z.; Wang, S.W.; Wang, J.T.; Peppe, C. Indium(III) bromide-catalyzed preparation of dihydropyrimidinones: Improved protocol conditions for the Biginelli reaction. *Tetrahedron* **2002**, *58*, 4801. [CrossRef]
27. Lu, J.; Bai, Y. Catalysis of the Biginelli Reaction by Ferric and Nickel Chloride Hexahydrates. One-Pot Synthesis of 3,4-Dihydropyrimidin-2(*1H*)-ones. *Synthesis* **2002**, *4*, 466. [CrossRef]
28. Reddy, C.V.; Mahesh, M.; Raju, P.V.K.; Babu, T.R.; Reddy, V.V.N. Zirconium(IV) chloride catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones. *Tetrahedron Lett.* **2002**, *43*, 2657. [CrossRef]
29. Prabhakar, A.S.; Dewkar; Sudalai, A. Cu(OTf)2: A reusable catalyst for high-yield synthesis of 3,4-dihydropyrimidin-2(*1H*)-ones. *Tetrahedron Lett.* **2003**, *44*, 3305.
30. Srisnivas Rao, A.; Varala, R.; Alam, M.M. Chemoselective Michael Type Addition of Aliphatic Amines to α,β-Ethylenic Compounds Using Bismuth Triflate Catalyst. *Synlett* **2003**, *5*, 720–722.
31. Maiti, G.; Kundu, P.; Guin, C. One-pot synthesis of dihydropyrimidinones catalysed by lithium bromide: An improved procedure for the Biginelli reaction. *Tetrahedron Lett.* **2003**, *44*, 2757. [CrossRef]
32. Wang, L.; Qian, C.; Tian, H.; Yun, M.A. Lanthanide Triflate Catalyzed One-Pot Synthesis of Dihydropyrimidin-2(*1H*)-thiones by a Three-Component of 1,3-Dicarbonyl Compounds, Aldehydes, and Thiourea Using a Solvent-Free Biginelli Condensation. *Syn. Comm.* **2003**, *33*, 1459. [CrossRef]
33. Shaabani, A.; Bazgir, A.; Teimouri, F. Ammonium chloride-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(*1H*)-ones under solvent-free conditions. *Tetrahedron Lett.* **2003**, *44*, 857. [CrossRef]
34. Salehi, H.; Guo, Q.X. A Facile and Efficient One-Pot Synthesis of Dihydropyrimidinones Catalyzed by Magnesium Bromide Under Solvent-Free Conditions. *Syn. Comm.* **2004**, *34*, 171.
35. Adharvana Chari, M.; Syamasundar, K.J. Silicagel supported sodium hydrogensulfate as a heterogenous catalyst for high yield synthesis of 3,4-dihydropyrimidin-2 (*1H*)-ones. *Mol. Catal. A* **2004**, *221*, 137. [CrossRef]
36. Ryabukin, S.V.; Plaskon, A.S.; Ostapehuk, E.N.; Volochnyuk, D.M.; Tolmachev, A.A. N-Substituted Ureas and Thioureas in Biginelli Reaction Promoted by Chlorotrimethyllsilane: Convenient Synthesis of *N*1-Alkyl-,and *N*1,N3-Dialkyl-3,4-Dihydropyrimidin-2(*1H*)-(thi)ones. *Synthesis* **2007**, 417–427.
37. Schauble, J.H.; Trauffer, E.A.; Deshpande, P.P.; Evans, R.D. Ruthenium(III) Chloride-Catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(*1H*)-ones under Solvent-Free Conditions. *Synthesis* **2005**, 1333–1339. [CrossRef]
38. Hazarkhani, H.; Karimi, B. 4. *N*-Bromosuccinimide as an Almost Neutral Catalyst for Efficient Synthesis of Dihydropyrimidinones under Microwave Irradiation. *Synthesis* **2004**, 1239–1242. [CrossRef]
39. Petersen, H. Syntheses of Cyclic Ureas by R-Ureidoalkylation. *Synthesis* **1973**, 243–292. [CrossRef]
40. Kappe, C.O.; Falsone, F.; Fabian, W.M.F.; Belaj, F. Isolation, Conformational Analysis and X-Ray Structure Determination of a Trifluoromethyl-Stabilized Hexahydropyrimidines An Intermediate in the Biginelli Reaction. *Heterocycles* **1999**, *51*, 77–84. [CrossRef]
41. Saloutin, V.I.; Burgat, Y.V.; Kuzueva, O.G.; Kappe, C.O.; Chupakhin, O.N. Biginelli Condensations of Fluorinated 3-Oxo Esters and 1,3-Diketones. *J. Fluorine Chem.* **2000**, *103*, 17–23. [CrossRef]