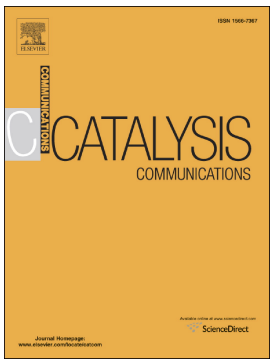

Evaluation of alcohols as substrates for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones under environmentally friendly conditions

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Evaluation of alcohols as substrates for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones under environmentally friendly conditions

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ABSTRACT

The aim of this research was to develop a procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones under environmentally friendly conditions using alcohols as the starting materials in aqueous media. The developed protocol resulted in 3,4-dihydropyrimidin-2(1H)-ones derivatives, which are relevant intermediates with therapeutic and pharmacological properties. Target products were synthetized in a tandem process, which meets the requirements of pharmaceutical chemistry. The influence of the reaction conditions was investigated, and as a result, various substituted 3,4-dihydropyrimidin-2(1H)-ones were obtained with a yield of up to 81%, free from heavy metal impurities.

Keywords: Biginelli reaction; tandem reaction; environmentally friendly conditions

1. Introduction

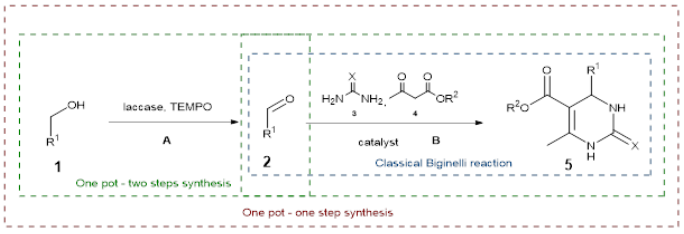
3,4-Dihydropyrimidin-2(1H)-ones (DHPMs) are well known for their biological and pharmacological properties such as antifungal[1], antiviral[2], cardiotropic[3], anti-inflammatory[4], hypotensive[3], antitumor[5], and antioxidant[6] activities. DHPMs can be obtained by a multicomponent reaction, discovered in the 19th century by Pietro Biginelli. This HCl-catalyzed reaction was carried out with an aldehyde, urea, and β-keto ester in ethanol. However, products were obtained with moderate yields (20-50%)[7]. To enhance the reaction yield, various methods have been elaborated, such as ultrasound irradiation[8]; usage of ionic liquids[9]; synthesis on the solid phase[10]; microwave irradiation[11]; and application of Lewis acid such as $Zn(OTf)_2$[12], $TaBr_5$[13], $Sr(OTf)_2$[14], and $RuCl_3$ [15] or Brønsted acid as a catalyst. Recently, Procopio *et al*. reported that $ErCl_3$ under microwave irradiation catalyzes the Biginelli reaction, providing products with high yield[16]. Nevertheless, the reported methods suffer from some drawbacks such as harsh reaction conditions, toxic and expensive catalysts, moderate yields, and tedious product isolation. Moreover, because of pharmaceutical requirements, the level of heavy metals must be maintained below 5 ppm[17], what makes the above-mentioned methods barely acceptable for this industry.

In chemical reactions, upon formation of the desired product, several by-products and impurities may be formed. In recent years, there has been significant increase in public awareness of the environmental issues in chemical syntheses. Therefore, a new type of chemical process that is green and environmentally friendly has become highly appreciated, where high emphasis is placed on the reduction of toxic wastes and solvents. As a result, new programs and principles are formulated, which support green chemistry, for example, "American Program Presidential Green Chemistry Challenge Awards Program"[18]. Enzymes are a sustainable catalyst that can be easily separated from products in contrast to the metal catalysts.

For example, it has been shown that lipases catalyze the Biginelli reaction providing desired products, DHPMs, with high yield (73-95%) in deep eutectic solvent (DES)[19]. Unfortunately, these solvents are expensive and toxic. The DHPM synthesis was also reported by Feng Xu *et al*., in which $CuCl_2$ x H_2O was applied as a catalyst under aqueous conditions[20]. Furthermore, it has been demonstrated that the application of surfactants such as sodium dodecyl sulfonate and sodium dodecyl sulfate has a beneficial effect on DHPM synthesis, leading to the substantial increase in the reaction yield. The application of the surfactants overcomes the main disadvantage of the low solubility of the organic compounds in aqueous medium[20,21].

Aldehydes among the other two urea and β-keto ester are the substrate for the Biginelli reaction. Unfortunately, aldehydes are highly reactive compounds that readily undergo oxidation, disproportionation, and aldol reaction[22]. Formation of the aldehydes in situ in the reaction mixture enables to overcome the drawback of their instability. The synthesis of aldehydes through the reduction of carboxylic acids or oxidation of alcohols may be not selective because of the possible over-reduction or over-oxidation. There are a number of reported protocols for the selective oxidation of alcohols to aldehydes using pure oxygen with $CuCl_2$/TEMPO/$NaNO_2$[23] or MNST (magnetic core-shell nanoparticle-supported TEMPO)/TBN system[24] or application of iodoxybenzoic acid (IBX)[25,26]. However, these reactions have some inconveniences such as harsh reaction conditions[27] and usage of carcinogenic organic solvents and toxic catalysts. In contrast to classical catalysts, laccases are enzymes that catalyze the oxidation of an alcohol to the corresponding aldehyde by atmospheric oxygen in the presence of a mediator under mild reaction conditions in aqueous solution[28]. It was emphasized in our previous works on tandem reactions in which alcohol was oxidized by laccase, followed by the subsequent Ugi[29] or Passerini[30] multicomponent reactions. Tandem processes connect several chemical transformations in one reaction vessel, what significantly simplifies and improves the overall synthesis[31].

The main idea of our studies was to develop an environmentally friendly one-pot protocol for the synthesis of the pharmaceutically relevant DHPMs. For the classical Biginelli reaction (highlighted in Scheme 1 as blue frame), an aldehyde is used as the starting material. Because of aldehyde instability, we have proposed a new approach toward target DHPMs, which is based on the chemoenzymatic tandem reactions that involve simultaneous in situ generation of an aldehyde from alcohols, followed by the Biginelli reaction. Two different synthetic approaches have been considered: (1) one pot–two step (reaction A followed by reaction B), and (2) one pot–one step (reactions A and B simultaneously). A schematic representation of these concepts is presented in Scheme 1.

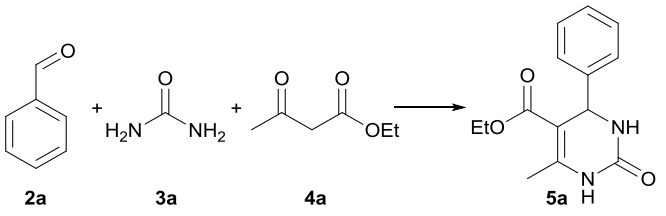


Scheme 1. Schematic representation of different approaches toward DHPMs. First: classical Biginelli reaction with aldehydes – blue frame. Second: one pot–one-step synthesis, which simultaneously combines alcohol oxidation and Biginelli reaction – red frame. Third: one pot–two-step synthesis, which connected oxidation reaction with subsequent Biginelli reaction separated in time – green frame.

2. Results and Discussion

To combine the alcohol oxidation to the corresponding aldehyde with Biginelli condensation in the same vessel, both transformations must share the same reaction medium. As the literature reports that the highest activity of laccase in the oxidation of alcohol to aldehydes was observed in phosphate buffer at pH = 5.2, this medium was used as the solvent for the subsequent Biginelli reaction [26]. First, a series of experiments were focused on finding an efficient catalyst for the Biginelli reaction, which promotes the reaction in selected media because there are no literature reports of Biginelli reaction in phosphate buffer at pH = 5.2. As model substrates for the Biginelli reaction, benzaldehyde (**2a**), urea (**3a**), and ethyl acetoacetate (**4a**) were selected. According to literature data, to reaction mixture SDS was added, as a surfactant, which overcomes the main disadvantage of the low solubility of organic compounds in phosphate buffer [20]. First, we investigated the influence of different types of catalysts such as enzymes, Brønsted acid, and Lewis acid on the Biginelli reaction course. The results are shown in Table 1.

Table 1. Investigation of catalyst for Biginelli reaction.



2a **3a** **4a** **5a**

Entry	Catalyst	Yield **5a** [5]
1	Laccase from *Trametes versicolor*	<1%
2	Lipase from *Rhizopus niveus*	2%
3	Lipase from *Mucor javanicus*	9%
4	Lipase from *Pseudomonas fluorescens*	2%
5	Lipase from porcine pancreas	3%
6	Citric acid	9%
7	$ZnCl_2$	9%
8	$FeCl_3$	17%
9	$Ce(SO_4)_2$	25%
10	$CuCl_2$	55%
11	$Cu(OAc)_2$	3%
12	CuO	<1%
13	CuI	<1%
14	$CuSO_4 \times 5H_2O$	57%

[a]Reaction conditions: 2a (1 mmol), 3a (1.5 mmol), 4a (1 mmol), SDS (0.2 mmol) catalyst (0.1 mmol or for enzymes 2 U/ml) and phosphate buffer pH = 5.2 (1.5 mL), 60 °C, 24 h.

As laccase from *Trametes versicolor* has copper atoms in its active site, it may catalyze oxidation reaction and Biginelli reaction at the same time[32]. However, it did not catalyze the Biginelli reaction (Table 1, entry 1). In addition, various lipases were tested as catalysts (Table 1, entries 2-5)[19]; this time, the desired product 5a was obtained with low yields of up to 9%. The reaction was carried out in the presence of citric acid (Table 1, entry 6), resulting in product 5a with a yield of 9%. Reaction in the presence of $ZnCl_2$, $FeCl_3$, or $Ce(SO_4)_2$ (Table 1, entries 7-9) resulted in product 5a with the maximum yield of 25%. When we used $Cu(OAc)_2$, CuO, or CuI (Table 1, entries 11-13), product 5a was obtained with quite low yield of less than 3%. Reaction carried out in the presence of $CuCl_2$ (Table 1, entry 10), which was reported in literature data[20], was less effective than that carried out with $CuSO_4 \times 5H_2O$ (Table 1, entry 14), which resulted in product **5a** with a yield of 57%. Our investigation revealed that $CuSO_4 \times 5H_2O$ is the most efficient catalyst. Therefore, it was consequently used for further studies.

Furthermore, to improve the reaction efficiency, the influence of an amount of $CuSO_4 \times 5H_2O$ on the yield of **5a** was tested. In the absence of the catalyst, the formation of the product **5a** was not observed. The reaction with **2a**, **3a,** and **4a** was performed in the presence of various amounts of $CuSO_4 \times 5H_2O$, and the yields of **5a** are presented in Figure S1 (Supplementary material). While upon increasing the amount of the catalyst from 1 to 20 mol%, the yield of the target product **5a** increased up to 82%, and further increase in the catalyst from 20 to 100 mol% did not enhance the reaction yield, what shows that 20 mol% $CuSO_4 \times 5H_2O$ was the optimal amount of catalyst, and it was consequently used throughout further studies.

Next, we investigated the influence of different types of surfactant such as cationic, anionic, amphoteric, and selected sugar esters on the model Biginelli reaction catalyzed by $CuSO_4 \times 5H_2O$ in PBS pH 5.2. Moreover, the application of biodegradable sugar esters, which were synthetized from renewable substrates using enzymes as catalysts under mild conditions, fulfilled the aspects of sustainable synthesis. The obtained results are presented in Table 2. Usage of hexadecylpyridinium chloride monohydrate (CPC) and Triton X-100 resulted in product **5a** with low yields, i.e., 33% or 24% (Table 2, entries 5 and 9). Dimethylmyristylammonio)propanesulfonate (SB3-14), dilauryldimethylammonium bromide (DDAB), hexadecylpyridinium chloride monohydrate (CTAB), Tween 80, 6-O-glucose 2-phenylacetate, 6-O-glucose 3-phenylpropionate, 6-O-glucose 4-phenylbutyrate, and 6-O-glucose 5-phenylpentate (Table 2, entries 2, 4, 6,10-14) did not significantly increase the yield of the desired product **5a**. Reaction carried out in the presence of 6-O-glucose laurate

(Table 2, entry 15) resulted in product **5a** with the yield of 59%. However, application of anionic surfactants such as sodium dodecyl sulfate (SDS) and dioctyl sulfosuccinate sodium salt (AOT) and cationic surfactants such as dimethyldioctadecylammonium bromide (DODAB) significantly increased the yield of product **5a** up to 82%. The collected results indicated that SDS is optimal for the tandem Biginelli reaction, and hence, it was used for further investigation (Table 2).

Table 2. Influence of the surfactant type on the yield of **5a**.[a]

Entry	R (acid)	Yield
1	---	51
2	SB3-14	47
3	DODAB	79
4	DDAB	48
5	CPC	33
6	CTAB	53
7	AOT	72
8	SDS	82
9	Triton X-100	24
10	Tween 80	56
11	6-O-glucose 2-phenylacetate	42
12	6-O-glucose 3-phenylpropionate	52
13	6-O-glucose 4-phenylbutyrate	48
14	6-O-glucose 5-phenylpentate	45
15	6-O-glucose laurate	59

[a] Reaction conditions: 2a (1 mmol), 3a (1.5 mmol), 4a (1 mmol), surfactant (0.2 mmol), $CuSO_4$ x $5H_2O$ (0.2 mmol) and phosphate buffer with pH 5.2 (1.5 mL) at 60 °C for 24 h.

Regarding the fact that the concentration of the surfactant has an impact on the reaction course[20], we investigated the influence of this factor (from 0 to 50 mol%) on the model Biginelli reaction. The results are presented in Figure S2 (Supplementary material). When the amount of SDS was changing from 0 to 20 mol%, the yield of the product increased to up to 82%. Further addition of SDS did not increase the reaction yield. On the basis of the obtained results, 20 mol% of SDS was selected as the optimal concentration and used consequently for further studies.

Furthermore, to improve the reaction yields, we revised the influence of temperature on the reaction yield. The results are presented in Figure S3 (Supplementary material). The yield of the model product **5a** increased with the increase in the temperature from 25 to 60 °C. However, further elevation of the temperature to above 60 °C significantly reduced the yield of product **5a**. When the temperature was changed, the value of the critical micelle concentration also changed[33], what explained the obtained results. Performed studies revealed that the optimal temperature for the Biginelli reaction performed in phosphate buffer was 60 °C and as one was used for further studies.

Having optimized reaction conditions for the Biginelli reaction, further studies were conducted under the chemoenzymatic tandem reaction using 1 mmol of alcohol as the substrate. The first attempt to combine both reactions on a tandem process was by adding all reagents together, not leading to obtaining the corresponding product **5a**. Our investigation showed that the oxidation reaction without connecting with the Biginelli reaction led to obtain aldehyde with quantitative yield. Therefore, we assessed the influence of reagents for the Biginelli reaction on the oxidation of alcohol, which are shown in Table 3.

Table 3. Impact of the Biginelli reagents on the enzymatic oxidation of benzyl alcohol.[a]

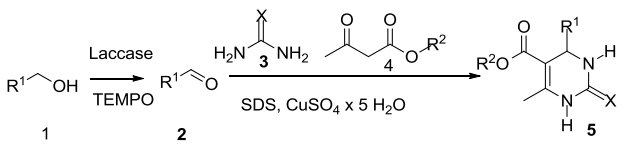
Entry	Reagents for Biginelli reaction	Amount of reagents for Biginelli reaction [mmol]	Yield of **2a** [%]
1	-	---	99
2	$CuSO_4$ x $5H_2O$	0.02	16
3	SDS	0.02	32
4	Urea	0.15	99
5	Ethyl acetoacetate	0.1	<1

Reaction conditions: laccase from *Trametes versicolor* (2 U/ml), benzyl alcohol (0.1 mmol), TEMPO (0.01 mmol), and phosphate buffer with pH 5.2 (150 µL) at 20 °C for 24 h. [a]. Determined by GC.

This research showed that $CuSO_4$ x H_2O, ethyl acetoacetate, and SDS significantly decreased the oxidation rate of benzyl alcohol. For this reason, the product **5** of the cascade reaction was not obtained in the one-step procedure; hence, we decided to separate both reactions by adding the rest of the reactants after the oxidation step. Oxidation of **1a** to aldehyde was catalyzed quantitatively by laccase from *Trametes versicolor* in the presence of TEMPO in phosphate buffer for 24 h at room temperature. Then, SDS, urea, $CuSO_4$ x $5H_2O$, and ethyl acetoacetate were added to the reaction mixture. Then, the reaction was continued for another 24 hours at 60 °C. The corresponding product **5a** was obtained with 48% yield. Subsequently, we investigated the influence of alcohol on the tandem process without changing the amount of other reagents. The obtained yields of **5a** are presented in Figure S4 (Supplementary material).

The results in Figure S4 indicated that when the amount of alcohol increased from 1 mmol to 1.5 mmol, the yield of product 5a in tandem one-pot process increased from 48% to 81%. Upon further increasing the amount of **1a,** the yield of the reaction decreased. Therefore, 1.5 mmol of alcohol was used to perform the subsequent reaction cascade.

Table 4. Scope and limitation of the chemoenzymatic Biginelli reaction.



Entry	R_1	R_2	X	Product	Yield [%]
1	C_6H_5	CH_2CH_3	O	5a	81
2	4-$CH_3C_6H_4$	CH_2CH_3	O	5b	75
3	4-FC_6H_4	CH_2CH_3	O	5c	34
4	4-ClC_6H_4	CH_2CH_3	O	5d	63
5	4-BrC_6H_4	CH_2CH_3	O	5e	81
6	4-$MeOC_6H_4$	CH_2CH_3	O	5f	52
7	4-$NO_2C_6H_4$	CH_2CH_3	O	5g	27
8	CH=CH-C_6H_5	CH_2CH_3	O	5h	80
9	$(CH_2)_{10}CH_3$	CH_2CH_3	O	5i	46
10	C_6H_5	$C(CH_3)_3$	O	5j	30
11	C_6H_5	$CH_2C_6H_5$	O	5k	41
12	C_6H_5	$(CH)_{11}CH_3$	O	5l	50
13	C_6H_5	CH_2CH_3	S	5m	0

Using different substrates, 12 compounds (5a-5l) were obtained, with yields ranging from 27% to 81%. Compounds **5a**, **5b**, **5e,** and **5h** were obtained with high yield of up to 75%. Benzyl alcohol derivatives that contain the halogen group have influence on the reaction yield. The more electronegative the halogen was, the lower the reaction yield was obtained (Table 4, entries 3-5), which was corresponding with the literature.[34] Low yield of compound **5i** may be caused by ineffective laccase-catalyzed oxidation. The laccase mainly catalyzes the oxidation of alcohols with an aromatic ring, and aliphatic alcohols are much worse substrates for it.[28] This newly developed procedure produces **5f**, which exhibits pharmaceutical properties.[35] The low yield of compound **5g** is also related to the low oxidation efficiency of p-nitrobenzylalcohol, and an unreacted substrate was found in the reaction mixture. The change of ethyl acetoacetate to another *β*-keto ester resulted in a significant decrease in reaction yield (Table 4, entries 1, 10-12). Products **5j**, **5k,** and **5l** were obtained with yields 30%, 41%, and 50%, respectively. Moderate yield of products **5j** and **5k** was attributed to spatial considerations. In the case of using thiourea under the developed conditions, the formation of the corresponding product was not observed (Table 4, entry 13).

3. Conclusions

A new environmentally friendly protocol for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) derivatives was proposed. Two different synthetic approaches were considered: (1) one pot–two step, and (2) one pot–one step. Our research revealed that the one pot-one step method does not provide target DHPMs because the laccase is inhibited by the substrates used for the Biginelli reaction. For these reasons, a tandem one pot–two step protocol based on the enzymatic oxidation of alcohol to aldehyde and subsequent Biginelli reaction in phosphate buffer was elaborated. Under the developed procedures, a series of new 3,4-dihydropyrimidin-2(1H)-ones derivatives were obtained with yields ranging from 27% to 81%. The presented protocol disclaims usage of flammable and toxic organic solvents, heavy and expensive metals, and explosive pure oxygen, what meet the requirements of pharmaceutical chemistry.

4. Experimental section

^{1}H NMR and ^{13}C NMR NMR spectra were recorded in acetone-D6 or DMSO-D6 with Bruker 400 MHz spectrometers. Tetramethylsilane (TMS) was used as internal standard. Gas chromatography were recorded on Clarus 680. High-resolution mass spectrometry (HRMS) spectra were recorded on an Mariner (PerSeptiveBiosystems) and Synapt G2:SHD apparatus. Melting points were determined with the model SMP-20 device (Büchi, Flawil, Switzerland). TLC was performed on Kieselgel 60 F254 aluminum sheets. Laccase from Trametes versicolor, powder, light brown, ≥0.5 U/mg was purchased from Sigma-Aldrich, product number 38429, lot number BCBQ2928V. The remaining starting materials of analytical grade were purchased from Sigma-Aldrich or TCI.

General procedure for the synthesis of compound 5. A mixture of laccase from *Trametes versicolor* (20 mg), benzyl alcohol (1.5 mmol), and TEMPO (16 mg) in phosphate buffer pH=5.2 (1.5 mL) was stirred at room temperature for 24 h. Then urea (1.5 mmol), ethyl acetoacetate (1 mmol), SDS (0.2 mmol), and $CuSO_4$ x $5H_2O$ (0.2 mmol) were added, and the reaction mixture was stirred at 60 °C for additional 24 h. In case of solid products (**5a, 5b, 5c, 5d, 5e, 5f, 5k, and 5l**), cold water (5 mL) was added to the reaction mixture and stirred for 10 min. The precipitate was filtered and washed with cold water (5 mL). Finally, the product was purified by recrystallization from ethanol. If the product was obtained as an oil (**5g, 5h, 5i, 5j**), then it was extracted with ethyl acetate (4 x 8 mL). Combined organic phases were dried with $MgSO_4$, and the crude product was purified by column chromatography (silica gel, AcOEt/hexane).

5. Acknowledgments

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Ryszard Ostaszewski for manuscript entitled „ E*valuation of alcohols as the substrates for the synthesis of 3,4-dihydropyrimidine-2(1H)-ones under environmentally friendly conditions*"; Ref. No.: CATCOM-D-19-00685R2.

Graphical abstract

Highlights

A new environmentally friendly method for the synthesis of DHPM was evaluated.

Two different synthetic approaches were considered.

A tandem one pot - two step protocol was elaborated.

Alcohols were enzymatically oxidized to aldehydes and used for subsequent Biginelli reaction.