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An efficient synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones catalyzed by thiamine hydrochloride in water under ultrasound irradiation

Priyanka G. Mandhane, Ratnadeep S. Joshi, Deepak R. Nagargoje, Charansingh H. Gill *

Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431 004, Maharashtra, India

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ABSTRACT

An environmentally benign aqueous Biginelli protocol for the synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-ones using thiamine hydrochloride as a catalyst has been achieved. These ultrasound-assisted reactions proceed efficiently in water in the absence of organic solvent. Utilization of ultrasound irradiation, simple reaction conditions, isolation, and purification makes this manipulation very interesting from an economic and environmental perspective.

1. Introduction

Organic transformations in aqueous media without using hazardous reagents or solvents are of interest.[1] In the past decade, dihydropyrimidinones (DHPMs) and their derivatives have attracted considerable interest because they exhibit promising activities as calcium channel blockers, antihypertensive agents, and as α-1a-antagonists and neuropeptide Y (NPY) antagonists.[2] Furthermore, several isolated bioactive marine alkaloids were also found to contain a 2-amino-1,4-dihydropyrimidinone-5-carboxylate core.[3] Most notable among them are batzalladine alkaloids, which have been found to be potent HIVgp-120-CD4 inhibitors.[4] Their derivatives exhibit a wide spectrum of biological effects including antifungal, antiviral, anticancer, antibacterial, anti-inflammatory, and antihypertensive effects.[5] Thus, a synthesis of this heterocyclic nucleus has been of much importance in current years.

A simple and direct method, originally reported by Biginelli,[6] for the synthesis of dihydropyrimidinones often suffers from low yields of products in the case of substituted aromatic and aliphatic aldehydes.[7] This has led to the recent disclosure of several one-pot methodologies for the synthesis of DHPM derivatives involving classical conditions, with microwave and ultrasound irradiation and by using Lewis acids as well as protic acid promoters such as $ZrCl_4$,[8] $CuCl_2{\cdot}2H_2O$–HCl,[9] LiBr,[10] $LaCl_3$–graphite,[11] $InBr_3$,[12] GaX_3,[13] $ZnBr_2$,[14] 1,1,3,3-tetramethylguanidinium trifluoroacetate,[15] $Cu(OTf)_2$,[16] [bmim] BF_4-immobilized Cu(II) acetylacetonate,[17] and [bmim] $[FeCl_4]$.[18] Recently, a base-catalyzed version of these reactions was reported in EtOH at reflux.[19] Modified syntheses of DHPMs have been advanced also in aqueous media.[20] However, more efficient syntheses of these biologically active compounds in aqueous media are important. However, all the existing methods displayed drawbacks, such as environmental pollution caused by utilization of organic solvents, long reaction time, exotic reaction conditions, unsatisfactory yields, and complicated operations. Therefore, it is urgent to further develop an efficient and convenient method to construct such significant scaffold.

Ultrasound-accelerated chemical reactions are well-known and proceed via the formation and adiabatic collapse of transient cavitation bubbles. Ultrasound irradiation has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to provide improved yields and increased selectivities.[21] Therefore, ultrasound irradiation has been established as an important technique in organic synthesis.[23]

The use of solid acid catalysts has gained a vast importance in organic synthesis due to their several advantages such as operationally simplicity, no toxicity, reusability, low cost, and ease of isolation after completion of the reaction. It is well-known that thiamine hydrochloride (VB1) is a cheap and non-toxic reagent. The structure of VB1 contains a pyrimidine ring and a thiazole ring linked by a methylene bridge (Fig. 1). The use of VB1 analogs as powerful catalysts for various organic transformations has been reported.[22] Herein, we report the thiamine hydrochloride-catalyzed greener synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones in aqueous

* Corresponding author. Tel.: +91 9822037127.
E-mail addresses: prof_gill@rediffmail.com, pgmandhane@gmail.com (C.H. Gill).

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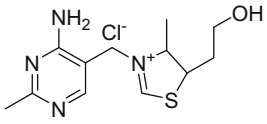


Figure 1. Structure of thiamine hydrochloride (VB1).

medium using ultrasound irradiation (Scheme 1). Compared with those methods mentioned above, our reactions displayed their advantages: (i) green synthesis without organic solvents is involved; (ii) shortened time and improved yields; and (iii) mild conditions and ready operations.

2. Results and discussion

In the current study, the commercially available catalyst thiamine hydrochloride is used as a catalyst for Bigenelli reaction. The use of VB1 catalyst under ultrasonic irradiation plays an important role in the synthesis and hence the reaction rate was improved and the reaction time was reduced. We have investigated the effect of different solvents on the reaction rate as well as on the yield of the products (Table 1). Initially, we have done this experiment under solvent-free condition but reaction did not proceed smoothly even after prolonged reaction time. The observations revealed that in aprotic solvents such as THF, DMF, and acetonitrile the product yield was found to be very low, but in case of protic solvent such as EtOH, MeOH, and water, the reaction rate as well as the product yield was found to be improved comparatively. After screening for different solvents, water was found to be the medium of choice, which afforded the products not only in good yield but also with higher reaction rates (94% yield in 15 min). We have also studied the sonochemical effect on model reaction by using diverse solvents. In all cases, the experimental results show that the reaction times are reduced and the yields of the products are higher under sonication. Based on the results of this study, it seems that the ultrasound irradiation improves the reaction times and yields. The obtained results are summarized in (Table 1, entries 1–7). Further we have studied the influence of catalyst concentration on the reaction time and percentage yield. As shown in Table 2, elevated amount of catalyst can improve the reaction yields and shorten the reaction time. However, in the absence of catalyst VB1, the reaction did not proceed even after extending reaction time, the results of which are summarized in (Table 2, entry 1). For example, when the catalyst concentration was 1 mol %, the yield was found to be 68% within 50 min (Table 1, entry 2), but when the catalyst concentration was increased to 5 mol %, the yield was found to be 94% within 15 min (Table 1, entry 6) under ultrasonic irradiation. Further increase in the concentration of catalyst did not improve the yields. Therefore, the one-pot condensation was carried out at 5 mol % of catalyst concentration.

We also examined the reaction on the aliphatic aldehydes, it gave the corresponding products in low yields after prolonged reaction time (Table 3, entries 11 and 12).

Table 1
Optimization of solvent effect on the model reaction[a]

Entry	Solvent	With US[a] yield[c] (%)	Without US[b] yield[c] (%)
1	Solvent free	25	
2	Dimethylformide	34	29
3	Acetonitrile	65	54
4	Tetrahydrofuran	67	56
5	Methanol	72	65
6	Ethanol	78	70
7	Water	94	86

[a] Reaction of benzaldehyde (2 mmol) with β-keto ester (2 mmol), urea (3 mmol), and thiamine hydrochloride (5 mol %) under ultrasonic waves for 20 min.
[b] Reaction of benzaldehyde with β-keto ester, urea, and thiamine hydrochloride (5 mol %) under constant stirring for 60 min.
[c] Isolated yield.

Table 2
Effect of catalyst concentration on model reaction[a]

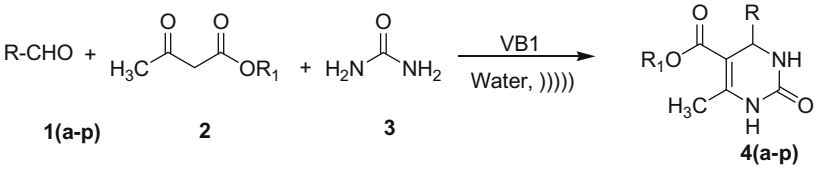
Entry	Catalyst (mol %)	Time[b] (min)	Yield[c] (%)
1	0	60	–
2	1.0	50	68
3	2.0	45	72
4	3.0	30	80
5	4.0	20	85
6	5.0	15	94
7	6.0	15	94

[a] Reaction of benzaldehyde with β-keto ester, urea, and thiamine hydrochloride (5 mol %) under ultrasonic irradiation.
[b] Time required.
[c] Isolated yield.

In conclusion, we have described a novel approach to explore the use of ultrasound irradiation for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones using thiamine hydrochloride (VB1) as a catalyst under aqueous condition at ambient temperature within 15–25 min. In the given approach, 2 mmol of substituted aldehydes react with β-keto ester (2 mmol), urea (3 mmol), and thiamine hydrochloride (5 mol %), and the formation of 3,4-dihydropyrimidin-2-(1*H*)-ones was observed in very high yield. We believe that sonochemical synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones using thiamine hydrochloride as a catalyst-promoted methodology will be a valuable addition to the existing processes in the field of 3,4-dihydropyrimidin-2-(1*H*)-ones (Table 3).

3. General procedure

A mixture of substituted aldehyde (**1**, 2 mmol), β-keto ester (**2**, 2 mmol), urea (**3**, 3 mmol), and thiamine hydrochloride (**4**, 5 mol %) was placed in a 50 ml round-bottomed flask. The mixture was irradiated in the water bath of an ultrasonic cleaner for a period as indicated in (Table 3) (sonication was continued until the aldehyde disappeared, as indicated by TLC). After completion of the reaction, the resulting suspension was filtered. The collected solid was filtered and recrystallized from ethanol to get the pure product. The products **4**(**a**–**p**) were confirmed by comparisons with authentic samples, IR, ^{1}H NMR, mass spectra, and melting point.



Scheme 1. Synthesis of various 3,4-dihydropyrimidin-2-(1*H*)-ones using VB1 as a catalyst.

Table 3
Ultrasound-promoted synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones catalyzed by VB1[a] (**4a**–**p**)

Entry	Aldehyde	R^1	Product	Time[b] (min)	Yield[c] (%)
1	Benzaldehyde	C_2H_5	**4a**[7b]	15	94
2	2-Chlorobenzaldehyde	C_2H_5	**4b**[25]	20	88
3	3-Chlorobenzaldehyde	C_2H_5	**4c**[26]	20	93
4	4-Chlorobenzaldehyde	C_2H_5	**4d**[24]	25	92
5	4-Methoxybenzaldehyde	C_2H_5	**4e**[7b]	15	82
6	2-Hydroxybenzaldehyde	C_2H_5	**4f**[7b]	20	85
7	4-Hydroxybenzaldehyde	C_2H_5	**4g**[7b]	15	90
8	3-Nitrobenzaldehyde	C_2H_5	**4h**[7b]	25	84
9	4-Nitrobenzaldehyde	C_2H_5	**4i**[7b]	15	88
10	4-Hydroxy-3-methoxy benzaldehyde	C_2H_5	**4j**[7b]	20	90
11	Acetaldehyde	C_2H_5	**4k**[25]	35	47
12	Butyraldehyde	C_2H_5	**4l**[25]	30	69
13	Benzaldehyde	CH_3	**4m**[24]	15	87
14	4-Chlorobenzaldehyde	CH_3	**4n**[24]	20	90
15	4-Methoxybenzaldehyde	CH_3	**4o**[24]	20	93
16	4-Nitrobenzaldehyde	CH_3	**4p**[24]	25	86

[a] Reaction of aldehyde with β-keto esters and urea in the presence of thiamine hydrochloride (5 mol %) in water under ultrasonic irradiation.
[b] Time required.
[c] Isolated yield. All the compounds characterized by their spectroscopy method ^{1}H NMR, mass, IR, and melting point from authentic sample.[27]

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27. Spectral data of selected compounds
Compound (**4b**): mp 252–254 °C; IR (KBr): 3215, 3080, 1687, 1641 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 2.31 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3), 5.71 (s, 1H, CH), 7.33–7.41 (m, 4H, Ar-H), 7.81 (s, 1H, NH), 9.15 (s, 1H, NH); MS: *m/z*: 281.3; (**4h**): mp 279–281 °C; IR (KBr): 3333, 3215, 1710, 1645 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.31 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 5.31 (s, 1H, CH), 7.71–8.16 (m, 4H, Ar-H), 7.85 (s, 1H, NH), 9.25 (s, 1H, NH); MS: *m/z*: 291.8; (**4i**): mp 205–207 °C; IR (KBr): 3217, 1731, 1711, 1652 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.16 (t, 3H, *J* = 6.9 Hz, CH_3), 2.31 (s, 3H, CH_3), 4.25 (q, 2H, OCH_2), 5.16 (s, 1H, CH), 7.81 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.81 (s, 1H, NH), 8.25 (d, 2H, *J* = 7.2 Hz, Ar-H), 9.33 (s, 1H, NH); MS: *m/z*: 291.8.