

Microwave-Assisted One-Pot Synthesis of Octahydroquinazolinone Derivatives Catalyzed by Thiamine Hydrochloride Under Solvent-free Condition

Pravin V Badadhe, Asha V. Chate, Dattatraya G. Hingane, Pravin S. Mahajan,
Namdev M. Chavhan, and Charansingh H. Gill*

Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431004.

*E-mail: chgill16@gmail.com

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ABSTRACT. Thiamine hydrochloride (VB1) has been used as an acid catalyst in organic synthesis. One pot three component Biginelli condensation of dimedone, urea/thiourea and substituted aromatic aldehydes catalyzed by 10 mol % of thiamine hydrochloride (VB1) in solvent free condition under microwave irradiation in good to excellent yields has been investigated. Utilization of microwave irradiation, simple reaction conditions, short reaction time, ease of product isolation, and purification makes this manipulation very interesting from an economic and environmental perspective.

Key words: Thiamine hydrochloride, Biginelli reaction, Octahydroquinazolinone derivatives, Microwave-irradiation, Solvent-free

INTRODUCTION

In recent years, Octahydroquinazolinone derivatives have attracted considerable attention in recent years owing to their potential antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *pseudomonas aeruginosa*¹ and also as a calcium antagonist.² Methods employed for their synthesis are the variant classical one pot multi-component Biginelli reaction involving dimedone, aromatic aldehydes and urea/thiourea³ There are very few reports for the synthesis of octahydroquinazolinone derivatives using catalysts such as TMSCl ,⁴ Nafion-H,⁵ $\text{Conc.H}_2\text{SO}_4$ ⁶ and ionic liquid $[\text{tbmim}]\text{Cl}_2/\text{AlCl}_3$.⁷ Octahydroquinazolinone derivatives also synthesized in absolute ethanol but with low yields of products (19-69 %). However many of these procedures suffer from one or more disadvantages such as harsh reaction conditions, prolonged reaction period, poor yields, use of hazardous and expensive catalysts, strongly acidic conditions and also suffer from the formation of many side products.⁸ So the development of clean, high-yielding and environmentally friendly approaches is still desirable and much in demand. Nowadays, an important development in the chemical industry is that many traditional chemical processing techniques are reaching their optimum performance, while consumer's demands stretch and governmental regulations tighten. Within the past 20 years, there has been a growing interest in new reaction conditions and activation methods, including 'dry conditions' (reactions

without solvent) and reactions under extreme or nonconventional conditions (high pressure, ultrasound or microwave irradiation). The effects usually expected are rate enhancements, yield and selectivity improvements, easier work-ups or less environmental polluting processes. Microwave heating makes it convenient to perform reactions very efficiently in the absence of any organic solvents, under so-called dry media conditions. The advantages of using dry media conditions go from faster reactions with different selectivity to more economical conditions due to the absence of organic solvents.⁹ They clearly constitute an eco-friendly 'green' approach.¹⁰ Literature survey reveals that a number of octahydroquinazolinone derivatives have been synthesized by Biginelli reaction conditions using various aldehydes but not a single reference have been found where microwave irradiation has been used for the synthesis of octahydroquinazolinone. 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. And so, we report an eco-friendly, facile and efficient methodology for the synthesis of octahydroquinazolinone by using thiamine hydrochloride (VB1). It is well known that vitamin (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.¹¹ Recently, we reported the

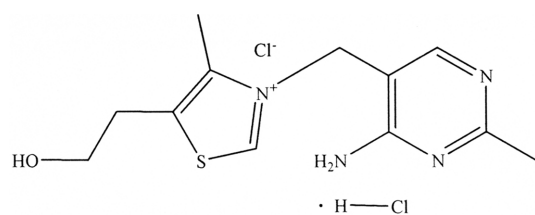
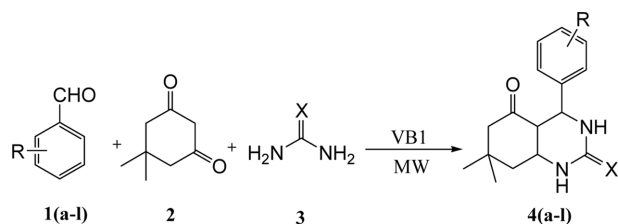


Fig. 1. Structure of thiamine hydrochloride (VB1).



Scheme 1. Synthesis of Octahydroquinazolinone.

thiamine hydrochloride catalyzed greener synthesis of octahydroquinazolinone in solvent free condition under MW irradiation (*Scheme 1*). Compared with those methods mentioned above, the present procedure using VB1 as catalyst provides an efficient one-pot synthesis of octahydroquinazolinone in solvent free condition under mw irradiation. The advantages of this procedure are operational simplicity, eco-friendly, availability of catalyst, cost effective and high yields. We believe that this method presents a practical alternative to existing procedures for the synthesis of octahydroquinazolinone.

RESULT AND DISCUSSION

In continuation of our research work on the development of novel methodologies¹² using ultrasonication and microwave irradiation techniques, herein we have developed methodology for the synthesis of octahydroquinazolinone in presence of thiamine hydrochloride (VB1) under microwave irradiation and solvent free condition (*Scheme 1*).

Here we carried out the reaction of benzaldehyde (1a),

Table 1. Screening of catalysts concentration on the model reaction^a

Entry	Catalysts	Time (min)	Yield ^b (%)
1	0	5	0
2	2	5	32
3	4	5	44
4	6	5	51
5	8	5	63
6	10	5	89
7	12	5	89

^aReaction of benzaldehyde, dimedone and urea in presence of thiamine hydrochloride under microwave-irradiation and solvent-free condition. ^bIsolated yield.

dimedone (2) and urea/thiourea (3) catalyzed by thiamine hydrochloride (VB1) under solvent free condition and microwave irradiation has been considered as a standard model reaction. We have studied the different reaction condition on model reaction. The result reveals that when the reaction was carried out at room temperature and reflux condition it gave lower yield of product even after prolonged reaction time. On the other hand when the reaction was carried out under microwave irradiation we obtained the desired product in high yields (82-92%) in short time (*Table 3*).

Firstly, we have studied the effect of catalyst concentration on model reaction. We have varied the concentration of catalyst to 2, 4, 6, 8, 10 and 12 mol%. The results revealed that, when the reaction was carried out in the absence of catalyst, the reaction did not proceed at all, whereas in the presence of 2, 4, 6, 8 mol% of catalyst it gave lower yield of product even after prolonged reaction time. At the same time when the concentration of catalyst was 10 mol% then we obtained the excellent yields of products in a short span. Even after increasing the catalyst concentration to 12 mol%, the yields of the products were found to be constant. So, the use of 10 mol% of catalyst appears to be optimal. The results obtained are summarized in (*Table 1*).

Table 2. Optimization of solvent effect on the model reaction

Entry	Solvent	With MW ^a		Without MW ^b	
		Time (min)	Yield ^c (%)	Time (min)	Yield ^c (%)
1	Water	5	25	120	20
2	Toluene	5	34	120	28
3	Dimethyl formamide	5	65	120	53
4	Acetonitrile	5	72	120	60
5	Solvent free	5	89	120	65

^aReaction of benzaldehyde, dimedone and urea in presence of thiamine hydrochloride (10 mol %) under microwave-irradiation for 5 minute.

^bReaction of benzaldehyde, dimedone and urea in presence of thiamine hydrochloride (10 mol %) under reflux condition for 120 minutes.

^cIsolated yield.

Table 3. Synthesis of octahydroquinazolinone derivatives catalyzed by thiamine hydrochloride under microwave-irradiation^a

Entry	Aldehydes	X	Time (min)	Yield ^b (%)	M.P. °C
4a	Benzaldehyde	O	3.5	89	291-292
4b	4-Chlorobenzaldehyde	O	4	82	>300
4c	4-Hydroxy-3-methoxy benzaldehyde	O	3	88	191-192
4d	4-Nitrobenzaldehyde	O	6	92	295-296
4e	4-Methoxybenzaldehyde	O	2.5	86	246-247
4f	3-Chlorobenzaldehyde	O	5	85	284-285
4g	4-Nitrobenzaldehyde	O	7	83	299-300
4h	4-Flurobenzaldehyde	O	4.5	88	135-136
4i	Benzaldehyde	S	11	87	281-282
4j	4-Methoxybenzaldehyde	S	13	83	271-272
4k	3-Chlorobenzaldehyde	S	14.5	85	277-278
4l	4-Bromobenzaldehyde	S	16	86	283-284

^aReaction Condition: **1** (**a-l**) (1 mmol), **2** (1 mmol), **3** (1.5 mmol) thiamine hydrochloride (10 mol%), under microwave-irradiation.

^bIsolated yield. All the products obtained were fully characterized by spectroscopic methods such as IR, ¹H NMR and mass¹⁴ and also compared with the reference compounds.¹⁴

Furthermore, we studied the effect of catalyst on different solvents for the synthesis of octahydroquinazolinone using thiamine hydrochloride and the results are summarized in (Table 2).

The result revealed that solvent free approach gives better results as compared to the reaction carried out in presence of various solvents. After optimizing the reaction conditions, the generality of this method was examined by the reaction of several substituted aldehydes, dimedone and urea/thiourea using thiamine hydrochloride as a catalyst in solvent free condition under microwave-irradiation; the results are shown in (Table 3).

Here, we have found that the reaction of aromatic aldehydes having electron-withdrawing groups reacted at faster rate as compared to aromatics aldehydes with electron releasing groups, unlike those of urea, the reaction of thiourea proceeded at lower rate, to give octahydroquinazolinone. The results obtained in the current method are illustrated in (Table 3. entry **4i-l**). We have tried this reaction on aliphatic aldehyde but we did not got satisfactory results. All the products thus obtained were fully characterized by spectroscopic methods such as IR, ¹H NMR and mass spectroscopy and also compared with the reference compound.¹⁴ As can be seen from (Table 3) it was found that the microwave irradiation was very simple and convenient for the synthesis of octahydroquinazolinone. It was observed that, the irradiation at low power requires longer time and at high power suffering from lower yield. So the irradiation at 360 W gives better results. The proposed reaction mechanism of the thiamine hydrochloride catalyzed Biginelli reaction includes the reaction of urea with aromatic aldehyde gives *N*-acylimin-

ium ion as a intermediate Then the interception of the iminium ion by dimedone presumably through its enol tautomer produces an open chain ureide which subsequently cyclized to hexahydroquinazolinones. Finally VB1 catalyzed elimination of water from hexahydroquinazolinones ultimately leads to the octahydroquinazolinone.¹³

CONCLUSIONS

In conclusion, thiamine hydrochloride is a readily available, non-toxic, inexpensive, and efficient catalyst for the synthesis of octahydroquinazolinone derivatives. The advantages offered by this method are solvent-free reaction conditions, short reaction times, ease of product isolation, and high yields. We believe that this environmental benign method is a useful addition to the present methodology for the synthesis of octahydroquinazolinone derivatives.

EXPERIMENTAL SECTION

All reagents were obtained from commercial suppliers and used without further purification. All melting points were determined in open capillaries and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel F254 plates from Merck and compounds visualized in UV light or either by exposure to iodine. Microwave oven (LG Smart Chef MS-255R operating at 2450 MHz having maximum out put power of 960 W) was used for microwave irradiation. ¹H NMR spectra were recorded on Mercury plus Varian at 400 MHz in

CDCl_3 as a solvent and TMS as an internal standard. Chemical shifts are reported in ppm (δ) and coupling constants (J) are given in Hz. IR spectra were recorded on a Perkin Elmer FTIR using KBr discs. Mass spectra were recorded on Micromass Quattro II using electrospray ionization technique.

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- Typical experimental procedure for octahydroquinazolinone*: A mixture of aromatic aldehydes. **1(a-l)**: (1 mmol), dimedone. **2**: (1mmol) urea/thiourea. **3**: (1.5 mmol), and thiamine hydrochloride (10 mol%) was mixed properly with the help of glass rod and irradiated in a microwave oven for appropriate time as indicated in Table 3. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 6:4). After completion of the reaction, the reaction mixture was cooled and ice cold water (25 mL) was added. The solid compound thus obtained was filtered and crystallized from absolute ethanol to afford the pure corresponding octahydroquinazolinone derivatives. **4(a-l)**: in excellent yields. All the products were characterized from their spectral data. Spectroscopic data. **(4a)**: IR (KBr) ν_{max} 3324 (br), 3254 (br), 2960 (br), 1708 (s), 1677 (s), 1610 (vs), 1447 (w), 1370 (s), 1230 (s), 763 (s), 689 (w), 564 (w), 486 (w), 429 (w) cm^{-1} . ^1H NMR (400MHz, DMSO, d_6), δ 0.94 (s, 3H, Me); 1.10 (s, 3H, Me); 2.20 (q, $J = 16.0\text{Hz}$, 2H, CH_2); 2.38 (q, $J = 16.7\text{ Hz}$, 2H, CH_2); 5.25 (d, $J = 2.8\text{ Hz}$, 1H, CH); 7.32-7.21 (m, 5H, Ar); 7.46 (s, 1H, NH); 9.38 (s, 1H, NH); MS (ESI) m/z 271 (M+1). **(4b)**: IR (KBr) ν_{max} 3247 (br), 2960 (br), 1697 (vs), 1612 (vs), 1487 (s), 1375 (s), 1239 (s), 807 (w), 763 (w), 566 (s), 509 (w) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , d_6), δ 0.95 (s, 3H, CH_3); 1.08 (s, 3H, Me); 2.19 (q, $J = 17.5\text{ Hz}$, 2H, CH_2); 2.37 (q, $J = 17.5\text{ Hz}$, 2H, CH_2); 5.30 (d, $J = 2.8\text{ Hz}$, 1H, CH); 7.19-7.30 (m, 4H, Ar); 7.54 (s, 1H, NH); 9.36 (s, 1H, NH); MS (ESI) m/z 305 (M+1). **(4j)**: IR (KBr) ν_{max} 3259 (br), 3160 (br), 2956 (br), 1642 (vs), 1584 (vs), 1376 (s), 1252 (m), 1170 (s), 1023 (m), 825 (w), 768 (w), 551 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , d_6), δ 0.97 (s, 3H, Me); 1.10 (s, 3H, CH_3); 2.16 (q, $J = 16.0\text{ Hz}$, 2H, CH_2); 3.11 (s, 2H, CH_2); 3.70 (s, 3H, OCH_3); 5.17 (d, $J = 2.7\text{ Hz}$, 1H, CH); 6.81 (d, $J = 8.7\text{Hz}$, 2H, Ar); 7.25 (d, $J = 8.6\text{ Hz}$, 2H, Ar); 9.42 (s, 1H, NH); 10.34 (s, 1H, NH); MS (ESI) m/z 317 (M+1).