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Thiamine hydrochloride (VB_1) as an efficient promoter for the one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones

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ABSTRACT

A facile, efficient, and environmentally friendly procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from isatoic anhydride, aldehyde, and ammonium acetate in the presence of thiamine hydrochloride (VB_1) in EtOH is described. The protocol proves to be efficient and environmentally benign in terms of high yields, ease of recovery, and reusability of catalyst.

2,3-Dihydroquinazolin-4(1*H*)-ones are an important class of heterocyclic compounds with a broad spectrum of pharmacological and biological activities, such as antibacterial, antifertility, antifungal, antitumor, and mono amine oxidase inhibitory activity.[1] Moreover, the quinazolinone core scaffold has been extensively utilized as a drug-like template in medicinal chemistry.[2] Therefore, much considerable attention has been devoted toward these heterocyclic compounds.

In the past few years, several methods for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones have been reported, which include: (i) the condensation reaction of anthranilamide with aldehyde or ketone using *p*-toluenesulfonic acids as a catalyst;[3] (ii) the reductive cyclization of *o*-nitrobenzamide or *o*-azidobenzamide with aldehydes or ketones using metallic samarium in the presence of iodine or SmI_2;[4] (iii) the condensation of isatoic anhydride, aldehydes, and ammonium acetate or primary amine in the presence of $SnCl_2$,[5] *p*-toluenesulfonic acid,[6] gallium(III) triflate,[7] montmorillonite K-10,[8] molecular iodine,[9] silica sulfuric acid,[10] $Zn(PFO)_2$,[11] ceric ammonium nitrate,[12] and MCM-41-SO_3H.[13]

Although, several modified methods under improved conditions have been reported, most of them are so far associated with one or more drawbacks, such as harsh reaction conditions, prolonged reaction times, high reaction temperature, poor isolated yields, the use of toxic organic solvents, and the use of expensive metal salts as catalysts. Hence, the development of efficient and convenient approach to construct this type of heterocyclic compounds is necessary.

It is well known that thiamine hydrochloride (VB_1) is a non-flammable, inexpensive, stable, and non-toxic reagent. The structure of VB_1 contains a pyrimidine ring and a thiazole ring linked by a methylene bridge (Fig. 1). VB_1 is an essential nutrient for all the animals which must be obtained from their diet. In mammals, the deficiency of VB_1 results in Korsakoff's syndrome, optic neuropathy, and a disease called beriberi that affects the peripheral nervous and/or cardiovascular system. VB_1 analogs as powerful catalysts have been applied in various organic transformations.[14] Recently, we have reported several VB_1-catalyzed reactions for the synthesis of heterocyclic compounds, such as pyrimidinones,[15] dihydropyridines,[16] 1,2-dihydro-naphth[1,2-*e*][1,3]oxazine-3-one,[17] and benzo[4,5]imidazo[1,2-*a*]pyrimidine.[18]

In continuation of our investigations on the applications of VB_1 in organic synthesis, herein we wish to report a facile, efficient, and environmentally friendly procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via one-pot three-component

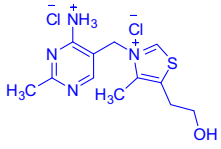

Figure 1. The structure of thiamine hydrochloride (VB_1).

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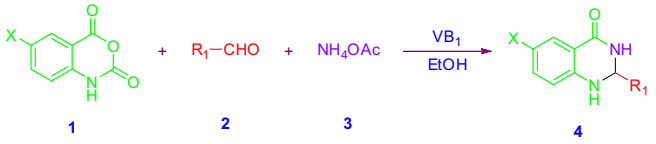
condensation reaction of isatoic anhydride, aldehydes, and ammonium acetate in excellent yields using VB_1 as a reusable catalyst in EtOH (Scheme 1).

Initially, we studied the three-component condensation reaction of isatoic anhydride **1a** (5 mmol), benzaldehyde **2a** (5.5 mmol), and ammonium acetate **3** (7.5 mmol) in 5 mL EtOH in the absence of VB_1 under reflux temperature for 6 h (Table 1, entry 1). However, only 20% yield of the corresponding product **4a** was obtained (Table 1, entry 1). Then, we carried out the reaction under similar conditions in the presence of 3 mol % of VB_1. To our delight, the product **4a** was obtained in 90% yield for 3 h (Table 1, entry 3). These results indicated that VB_1 could be used as an efficient catalyst for the condensation of isatoic anhydride **1**, benzaldehyde **2a**, and ammonium acetate **3** to synthesise 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one **4a**. Further investigation revealed that 3 mol % VB_1 was sufficient to catalyze this reaction. The excess amount of VB_1 could not increase the yields of the reaction significantly.

The activity of the recycled VB_1 was also examined according to the typical experiment conditions. After the reaction was completed as indicated by TLC, the target product **4a** was collected by simple filtration and washed with ethanol after cooled to the room temperature. Then, the filtered solution containing the catalyst was further treated with the reactants. It was shown that the catalyst could be used for three runs without significant drop in the product yields (Table 1, entry 3). Hence, this result demonstrated that VB_1 could be effectively used as a reusable catalyst for this multi-component condensation without any treatment.

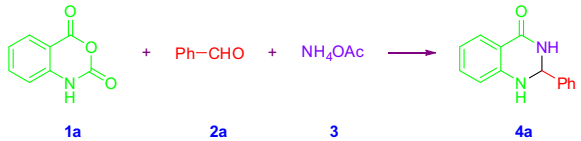
In order to study the generality of this condensation reaction, a series of 2,3-dihydroquinazolin-4(1*H*)-ones were synthesized from isatoic anhydride **1**, aldehydes **2**, and ammonium acetate **3** in the presence of 3 mol % VB_1 in EtOH at reflux temperature (Table 2).[19]

As shown in Table 1, this three-component condensation could proceed in the presence of 3 mol % VB_1 to obtain the 2,3-dihydroquinazolin-4(1*H*)-ones **4** in good yields (80–94%). The aromatic aldehydes bearing substitutions at *ortho*-, *meta*-, and *para*-positions participated well in this reaction (Table 2).



Scheme 1. VB_1-catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **4**.

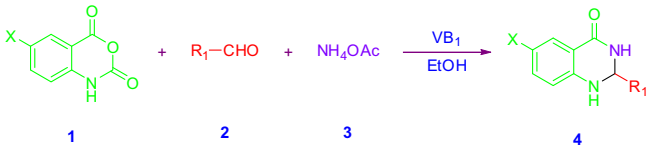
Table 1
Optimization of the reaction conditions[a]



Entry	Cat. (mol %)	Time (h)	Yield of **4a**[b] (%)
1	None	6	20
2	VB_1 (1)	6	60
3[c]	VB_1 (3)	3	90, 88, 86
4	VB_1 (5)	3	90
5	VB_1 (8)	3	88
6	VB_1 (10)	3	91

[a] Conditions: isatoic anhydride **1a** (5 mmol), benzaldehyde **2a** (5.5 mmol), ammonium acetate **3** (7.5 mmol), EtOH (5 mL), reflux.
[b] Isolated yields.
[c] Catalyst was reused for three times.

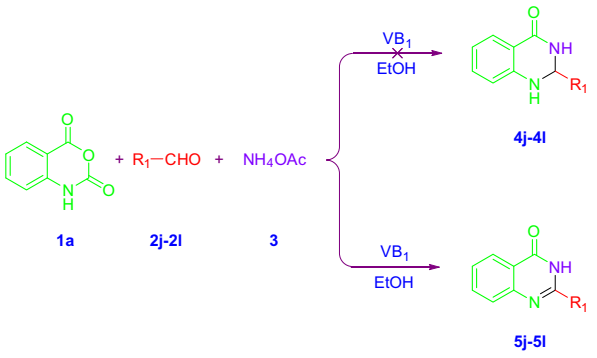
Table 2
Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **4** catalyzed by VB_1[a]



Entry	X	R_1	Time (h)	Product **4**	Yield of **4** (%)[b]
1	H	C_6H_5 **2a**	3	**4a**	90
2	H	4-ClC_6H_4 **2b**	3	**4b**	85
3	H	3-ClC_6H_4 **2c**	4	**4c**	80
4	H	2-ClC_6H_4 **2d**	6	**4d**	75
5	H	4-$MeOC_6H_4$ **2e**	3	**4e**	90
6	H	4-MeC_6H_4 **2f**	3	**4f**	90
7	H	3-MeO-4-OHC_6H_3 **2g**	5	**4g**	84
8	H	3,4-$(MeO)_2C_6H_3$ **2h**	3	**4h**	94
9	H	4-$MeOOCC_6H_4$ **2i**	2	**4i**	80
10	Cl	C_6H_5 **2a**	3	**4m**	88
11	Cl	4-$MeOC_6H_4$ **2e**	3	**4n**	85

[a] Conditions: isatoic anhydride **1** (5 mmol), aldehyde **2** (5.5 mmol), ammonium acetate **3** (7.5 mmol), VB_1 (0.15 mmol, 3 mol %), and EtOH (5 mL), reflux.
[b] Isolated yields.

Table 3
Synthesis of quinazolin-4(3*H*)-ones **5** catalyzed by VB_1[a]



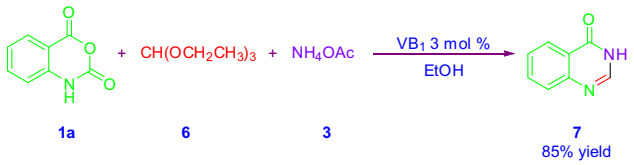
Entry	R_1	Time (h)	Product **5**	Yield of **5**[b] (%)
1	3,4,5-$(MeO)_3C_6H_2$ **2j**	4	**5j**	80
2	4-$NO_2C_6H_4$ **2k**	3	**5k**	82
3	3-CNC_6H_4 **2l**	4	**5l**	92

[a] Conditions: isatoic anhydride **1a** (5 mmol), aldehyde **2** (5.5 mmol), ammonium acetate **3** (7.5 mmol), VB_1 (0.15 mmol, 3 mol %), and EtOH (5 mL), reflux.
[b] Isolated yields.

Furthermore, we also used 3,4,5-trimethoxybenzaldehyde **2j**, 4-nitrobenzaldehyde **2k**, and 4-cyanobenzaldehyde **2l** as the substrates to synthesise 2,3-dihydroquinazolin-4(1*H*)-ones **4j–4l**. To our surprise, the products quinazolin-4(3*H*)-ones **5j–5l**, shown in Table 3 and confirmed by NMR measurements, were obtained, while in contrast, the desired product 2,3-dihydroquinazolin-4(1*H*)-ones **4j–4l** were not obtained. The probable reason for these results is that 2,3-dihydroquinazolin-4(1*H*)-ones **4j–4l** are easy to be oxidized by air to form quinazolin-4(3*H*)-ones **5j–5l**.[20]

As shown in Scheme 2, the condensation of isatoic anhydride **1a**, triethyl orthoformate **6**, and ammonium acetate **3** was studied in the presence of 3 mol % VB_1. The reaction could proceed smoothly to obtained the quinazolin-4(3*H*)-one **7** in 85% yield.[21]

In summary, the present method discloses a facile, efficient, and environmentally friendly procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via one-pot three-component condensation of isatoic anhydride **1**, aldehydes **2**, and ammonium acetate **3**



Scheme 2. VB_1-catalyzed synthesis of quinazolin-4(3*H*)-one **7**.

in the presence of 3 mol % VB_1 in EtOH. Furthermore, quinazolin-4(3*H*)-one **5** is obtained when 3,4,5-trimethoxybenzaldehyde **2j**, 4-nitrobenzaldehyde **2k**, 4-cyanobenzaldehyde **2l**, and triethyl orthoformate **6** are used as the substrates. The mild reaction conditions, high yields of the products, ease of work-up, and the ecologically clean procedure, will make the present method a useful and important addition to the present methodologies.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.090.

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19. General procedure for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones **4** using VB_1 as a catalyst: A mixture of isatoic anhydride **1** (5 mmol), aldehydes **2a–2i** (5.5 mmol), ammonium acetate **3** (7.5 mmol), and VB_1 (0.15 mmol, 3 mol %) in EtOH (5 mL) was heated to reflux for 3–6 h. After completion of the reaction (TLC), the solid was filtered off, washed with EtOH, and recrystallized from EtOH (5 mL) to yield pure product **4**.
4a: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.75 (s, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 7.12 (s, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.33–7.42 (m, 3H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 1H), 8.30 (s, 1H); MS (ESI): *m*/*z* 225 ([M+H]$^+$).
4e: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.75 (s, 3H), 5.70 (s, 1H), 6.67(t, *J* = 7.4 Hz, 1H), 6.74(d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 7.02 (s, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 7.7 Hz, 1H), 8.19 (s, 1H); MS (ESI): *m*/*z* 255 ([M+H]$^+$).
4i: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.85 (s, 3H), 5.85 (s, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 7.23 (s, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.98 (d, *J* = 8.2 Hz, 2H), 8.42 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.34, 69.04, 117.61, 118.05, 120.44, 130.32, 130.52, 132.31, 132.75, 136.58, 150.12, 150.68, 166.54, 169.09; MS (ESI): *m*/*z* 283 ([M+H]$^+$); HRMS (ESI) calcd for $C_{16}H_{15}N_2O_3$ [M+H]$^+$ 283.1077, found 283.1071.
20. General procedure for the preparation of quinazolin-4(3*H*)-ones **5** using VB_1 as a catalyst: A mixture of isatoic anhydride **1** (5 mmol), aldehydes **2j–2l** (5.5 mmol), ammonium acetate **3** (7.5 mmol), and VB_1 (0.15 mmol, 3 mol %) in EtOH (5 mL) was heated to reflux for 3–4 h. After completion of the reaction (TLC), the solid was filtered off, washed with EtOH, and recrystallized from EtOH (5 mL) to yield pure product **5**.
5j: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.75 (s, 3H), 3.91 (s, 6H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.57 (s, 2H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.84 (t, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 12.54 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.59, 60.62, 105.62, 121.30, 126.33, 126.97, 127.96, 128.12, 135.12, 140.66, 149.15, 152.16, 153.34, 162.79; MS (ESI): *m*/*z* 313 ([M+H]$^+$); HRMS (ESI) calcd for $C_{17}H_{17}N_2O_4$ [M+H]$^+$ 313.1183, found 313.1177.
5k: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.59 (t, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.37–8.45 (m, 4H), 12.87 (s, 1H); MS (ESI): *m*/*z* 268 ([M+H]$^+$).
21. General procedure for the preparation of quinazolin-4(3*H*)-one **7** using VB_1 as a catalyst: A mixture of isatoic anhydride **1** (5 mmol), triethyl orthoformate **6** (6 mmol), ammonium acetate **3** (7.5 mmol), and VB_1 (0.15 mmol, 3 mol %) in EtOH (5 mL) was heated to reflux for 4 h. After completion of the reaction (TLC), the solid was filtered off, washed with EtOH, and recrystallized from EtOH (5 mL) to yield pure product **7**.