Thiamine hydrochloride (VB\textsubscript{1}) as an efficient promoter for the one-pot synthesis of 2,3-dihydroquinazolin-4(1\textsubscript{H})-ones

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\textbf{Article info}

\textbf{Article history:}
Received 2 May 2012
Revised 20 August 2012
Accepted 23 August 2012
Available online 30 August 2012

\textbf{Keywords:}
Thiamine hydrochloride (VB\textsubscript{1})
Isatoic anhydride
Aldehyde
Dihydroquinazolin-4(1\textsubscript{H})-one
Green chemistry

\textbf{Abstract}

A facile, efficient, and environmentally friendly procedure for the synthesis of 2,3-dihydroquinazolin-4(1\textsubscript{H})-ones from isatoic anhydride, aldehyde, and ammonium acetate in the presence of thiamine hydrochloride (VB\textsubscript{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\textsubscript{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.\textsuperscript{1} Moreover, the quinazolinone core scaffold has been extensively utilized as a drug-like template in medicinal chemistry.\textsuperscript{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\textsubscript{H})-ones have been reported, which include: (i) the condensation reaction of anthranilamide with aldehyde or ketone using \textit{p}-toluenesulfonic acids as a catalyst;\textsuperscript{3} (ii) the reductive cyclization of \textit{o}-nitrobenzamide or \textit{o}-azidobenzamide with aldehydes or ketones using metallic samarium in the presence of iodine or \textit{SmI}_2;\textsuperscript{4} (iii) the condensation of isatoic anhydride, aldehydes, and ammonium acetate or primary amine in the presence of \textit{SnCl}_2,\textsuperscript{5} \textit{p}-toluenesulfonic acid,\textsuperscript{6} gallium(\textit{II}) triflate,\textsuperscript{7} montmorillonite K-10,\textsuperscript{8} molecular iodine,\textsuperscript{9} silica sulfuric acid,\textsuperscript{10} \textit{Zn}(PF\textsubscript{6})\textsubscript{2},\textsuperscript{11} ceric ammonium nitrate,\textsuperscript{12} and MCM-41-SO\textsubscript{3}H.\textsuperscript{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\textsubscript{1}) is a non-flammable, inexpensive, stable, and non-toxic reagent. The structure of VB\textsubscript{1} contains a pyrimidine ring and a thiazole ring linked by a methylene bridge (Fig. 1). VB\textsubscript{1} is an essential nutrient for all the animals which must be obtained from their diet. In mammals, the deficiency of VB\textsubscript{1} results in Korsakoff's syndrome, optic neuropathy, and a disease called beriberi that affects the peripheral nervous and/or cardiovascular system. VB\textsubscript{1} analogs as powerful catalysts have been applied in various organic transformations.\textsuperscript{14} Recently, we have reported several VB\textsubscript{1}-catalyzed reactions for the synthesis of heterocyclic compounds, such as pyrimidinones,\textsuperscript{15} dihydropyridines,\textsuperscript{16} 1,2-dihydro-naphth[1,2-e][1,3]oxazine-3-one,\textsuperscript{17} and benzo[4,5]imidazo[1,2-e]pyrimidine.\textsuperscript{18}

In continuation of our investigations on the applications of VB\textsubscript{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\textsubscript{H})-ones via one-pot three-component...
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 % 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(1H)-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(1H)-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).

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(1H)-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).

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol %)</th>
<th>Time (h)</th>
<th>Yield of 4a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>VB$_1$ (1)</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>VB$_1$ (3)</td>
<td>3</td>
<td>90, 88, 86</td>
</tr>
<tr>
<td>4</td>
<td>VB$_1$ (5)</td>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>VB$_1$ (8)</td>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>VB$_1$ (10)</td>
<td>3</td>
<td>91</td>
</tr>
</tbody>
</table>

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

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R$_1$ Time (h)</th>
<th>Product 4</th>
<th>Yield of 4 (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>C$_6$H$_5$ 2a</td>
<td>3</td>
<td>4a</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>4-ClC$_6$H$_4$ 2b</td>
<td>3</td>
<td>4b</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>3-ClC$_6$H$_4$ 2c</td>
<td>4</td>
<td>4c</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>2-ClC$_6$H$_4$ 2d</td>
<td>6</td>
<td>4d</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>4-MeOCH$_2$ 2e</td>
<td>3</td>
<td>4e</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>4-MeC$_6$H$_4$ 2f</td>
<td>3</td>
<td>4f</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>3-MeO-4-CHOCH$_3$ 2g</td>
<td>5</td>
<td>4g</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>3,4-(MeO)$_2$C$_6$H$_4$ 2h</td>
<td>3</td>
<td>4h</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>4-MeOOC$_6$H$_4$ 2l</td>
<td>2</td>
<td>4i</td>
</tr>
<tr>
<td>10</td>
<td>Cl</td>
<td>C$_6$H$_5$ 2a</td>
<td>3</td>
<td>4m</td>
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<tr>
<td>11</td>
<td>Cl</td>
<td>4-MeOCH$_2$ 2e</td>
<td>3</td>
<td>4n</td>
</tr>
</tbody>
</table>

* 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.
* 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(1H)-ones 4j–4l. To our surprise, the products quinazolin-4(3H)-ones 5j–5l, shown in Table 3 and confirmed by NMR measurements, were obtained, while in contrast, the desired product 2,3-dihydroquinazolin-4(1H)-ones 4j–4l were not obtained. The probable reason for these results is that 2,3-dihydroquinazolin-4(1H)-ones 4j–4l are easy to be oxidized by air to form quinazolin-4(3H)-ones 5j–5l.

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 obtain the quinazolin-4(3H)-one 7 in 85% yield.

In summary, the present method discloses a facile, efficient, and environmentally friendly procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones via one-pot three-component condensation of isatoic anhydride 1, aldehydes 2, and ammonium acetate 3.
in the presence of 3 mol % VB1 in EtOH. Furthermore, quinazolin-4(3H)-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 eco-logically clean procedure, will make the present method a useful and important addition to the present methodologies.

Acknowledgments
This work was supported by the National Natural Science Foundation of China (Grants 30925040, 81102329), the Chinese National Science & Technology Major Project “Key New Drug Creation and Manufacturing Program” (Grant 2011ZX09307-002-03), and the Science Foundation of Shanghai (Grant 12XD14057).

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.

References and notes
19. General procedure for the preparation of 2,3-dihydroquinazolin-4(1H)-ones 4 using VB1 as a catalyst: A mixture of isatoic anhydride 1 (5 mmol), aldehydes 2a–2l (5.5 mmol), ammonium acetate 3 (7.5 mmol), and VB1 (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.
20. General procedure for the preparation of quinazolin-4(3H)-ones 5 using VB1 as a catalyst: A mixture of isatoic anhydride 1 (5 mmol), aldehydes 2a–2l (5.5 mmol), ammonium acetate 3 (7.5 mmol), and VB1 (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.
21. General procedure for the preparation of quinazolin-4(3H)-one 7 using VB1 as a catalyst: A mixture of isatoic anhydride 1 (5 mmol), triethyl orthoformate 6 (6 mmol), ammonium acetate 3 (7.5 mmol), and VB1 (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.