Boric acid catalyzed one-pot synthesis of [1,2,4] triazolo quinazolinone Derivatives

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Abstract: We present a rapid, efficient one pot synthesis of [1,2,4]triazolo [5,1-b]quinazolin- 8(4H)-one derivatives by condensation of 3-amino-1,2,4-triazole with aldehydes and dimerdone in the presence of boric acid (5 mmol%) as a catalyst. This protocol corresponds in short reaction time, low cost, high reaction yield, no need of chromatographic separation with green aspects by using water soluble catalysts.

Keywords: aldehyde, 3-amino-1,2,4-triazole, dimerdone, boric acid.

I. Introduction

Multicomponent reactions (MCRs) in which three or more reactants are combined to form a product containing substantial elements of all reactants 1, 2. One pot MCR process have an efficient and powerful tool for the construction of complex molecules 3, 4. One pot MCR provides many chemical reactions which attributes such as minimization of use of silica gel for chromatographic purification of intermediate compounds, use of solvent 5. MCR’s have been exploited as a powerful tool for the assembly of large library of biologically active molecules 6. Nitrogen containing heterocyclic, triazole quinazolinone ring system exhibit biological activities such as antihypertensive 7, antihistaminic 8, analgesic, anti-inflammatory 9, anticancer 10 and anti-HIV activities 11. More over many naturally occurring and synthetic compounds containing triazole derivatives scaffold also posses interesting diverse pharmaceutical, agrochemical properties. Some important drugs which are present in market such as terconazole, alperazolame, triazolame and rizatRIPTAN 11b (figure 1) contains 1,2,4 Triazole nucleus. A three component condensation of a substituted aldehyde, dimerdone and 3-amino-1,2,4-triazole as an amine source is well known. An important existing procedure for the synthesis of 1,2,4-triazolo[5,1-b]quinolin-8(4H)-one derivatives have been carried out by refluxing starting compounds in DMF 12a,b, using sulphamic acid in acetonitrile as a solvent and reflux condition 13, ionic liquids 14, hetero polyacids 15, molecular iodine 16.

However some of these methodologies have many limitations of harsh reaction condition, use of expensive catalysts, long reaction time and tedious work up, low yield. Hence the development of rapid, simple, efficient, clean, high yielding, environmentally benign protocol using new catalyst for the synthesis of this compound is desirable. Boric acid is a water soluble inexpensive, stable, readily available, easy to handle catalyst and has been found effective in various transformations such as synthesis of aza Michael 17, thia Michael 18, transesterification of ethylacetocetate 19, synthesis of α-hydroxamides 20, bromination, oxidation of sulphides 21, bigenelli reaction 22, 1,5- benzodiazepine derivatives 22, 2-amino,3-5 dicarbonitrile-6-thio-pyridene 23. It is therefore important to examine the behavior of boric acid as a catalyst in the synthesis of 1,2,4-triazolo quinolinone derivatives.

Scheme : Synthesis of 1,2,4-triazolo[5,1-b]quinolin-8(4H)-one derivatives

To determine the optimum concentration of the boric acid catalyst, we investigated model reaction at it’s different concentrations. The product was formed in 91.2%, 98.2%, 96.1%, 89.7% and 83.5% (Table 1)
yield by using concentration of boric acid catalyst i.e. 3, 5, 10, 15, 20 mmol% respectively. These result shows 5mol% of boric acid is sufficient to carry out the reaction smoothly. Herein we report a synthesis of 1,2,4-triazolo[5,1-b]quinolin-8(4H)-one derivatives.

![Terconazole](image1.png) ![Alprazolam](image2.png) ![Triazolam](image3.png) ![Rizatriptan](image4.png)

**Figure 1**

**II. Experimental**

All solvents and chemicals which are used in this reaction are of commercial grade quality without any purification and were produced from Merck(Germany). Silica gel coated aluminium sheets (merck product) were used for thin layer chromatography to monitor progress of the reaction. Melting points were measured by an open capillary tube method and are uncorrected. $^1$H and $^{13}$C NMR were carried out on a SpectronicGenesys - 2 Spectrophotometer 300MHz in DMSO-d$_6$ solvent. IR spectra recorded from KBr disk in the range of 4000-200 cm$^{-1}$ on the Shimadzu FTIR spectrometer (Model no. 8400). MASS spectra were obtained on Polaris-Q Thermospecific GC-MS.


The mixture of 3-amino-1,2,4-triazole 3 (1mmol), p-nitro benzaldehyde (1mmol), dimedone 2 (1mmol) and 5mmol% boric acid was taken in an agate mortar and pestle set and ground it for 2 minutes. Then 5ml ethyl acetate was added to the mixture. After evaporation of the solvent product was separated out and washed with water then dried at low pressure to obtain the crude product. Completion of the reaction was monitored by TLC. The product was purified by recrystallization by using ethyl alcohol as a solvent to get expected product 4a-k.

All the compounds were synthesized and characterized using their data in literature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boric Acid (mmol%)</th>
<th>Yield$^b$</th>
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<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>83</td>
</tr>
</tbody>
</table>

Note: Bold values indicate optimized condition

$^a$Reaction condition: 1a(1mmol), 2(1mmol) and 3(1mmol) ground in agate mortar, rt

$^b$Isolated yield.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehydes(1)</th>
<th>Product(4)</th>
<th>% Yield$^c$</th>
<th>M.P. (°C)</th>
</tr>
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<tbody>
<tr>
<td>4a</td>
<td><img src="image5.png" alt="image5.png" /></td>
<td><img src="image6.png" alt="image6.png" /></td>
<td>9</td>
<td>304-306</td>
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>300$^{15}$

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<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Data</th>
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<td>4b</td>
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<td>4c</td>
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<td>85 291-293 289-290&lt;sup&gt;16&lt;/sup&gt;</td>
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<td>4f</td>
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<td>4g</td>
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<td><img src="4k.png" alt="Structure" /></td>
<td>92 227-229 228-230&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
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</table>

2.1. Spectroscopic Data for representative and newly synthesized compounds is listed below:
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6,6-Dimethyl-9-(4-nitro-phenyl)-5,6,7,9-tetrahydro-4H-1,2,4-triazolo[5,1-b]quinazolin-8-one (4a):
Pale yellow solid; Yield: 98.2%. M.P.=304–306°C. IR: 2962, 1645, 1568, 1354, 1250, 720 cm⁻¹; ¹H-NMR (DMSO-d₆, 300MHz): δH 1.02 (s, 3H, CH₃), 1.10 (s, 3H, CH₃), 2.10 (d, J=16.20 Hz, 2H), 2.30 (d, J=16.0 Hz, 2H), 2.55 (d, J=16.20 Hz), 6.35 (s, 1H), 7.14 (d, J=8.2 Hz, 2H), 7.61 (d, J=8.2 Hz, 2H), 8.04 (s, 1H), 11.03 (s, 1H, NH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 190.32, 155.21, 132.11, 130.11, 120.47, 112.42, 68.72, 66.46, 25.19, 17.21. MS m/z (ESI): 340 [M+H⁺].

6,7-dihydro-9-(2,4-dihydroxyphenyl)-6,6-dimethyl-[1,2,4]triazolo[5,1-b]quinazolin-8(4H,5H,9H)-one (4d):
Pale yellow solid; Yield: 83.7%. M.P.=294–296°C. IR: 3089, 2938, 1663, 1567, 1342, 1260, 788 cm⁻¹; ¹H-NMR (DMSO-d₆, 300MHz): δH 1.21 (s, 3H, CH₃), 1.23 (s, 3H, CH₃), 2.10 (q, J=13.8, 16.89 Hz, 2H, –CH₂), 2.84 (s, 3H, –CH₃), 6.87 (s, 1H, –CH), 7.30–7.36 (m, 2H, Ar-H), 7.51 (s, 1H, Ar-H), 7.59 (s, 1H, Ar-H), 8.19 (s, 1H, NH), 11.15 (s, 1H, NH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 162.87, 142.13, 130.76, 126.94, 123.31, 112.23, 60.89, 58.51, 14.83, 12.72. MS m/z (ESI): 311 [M+H⁺].

6,7-dihydro-9-(2-hydroxyphenyl)-6,6-dimethyl-[1,2,4]triazolo[5,1-b]quinazolin-8(4H,5H,9H)-one (4f):
Pale yellow solid; Yield: 91.4%. M.P.=287–290°C. IR: 3081, 2968, 1655, 1589, 1375, 1254, 764 cm⁻¹; ¹H-NMR (DMSO-d₆, 300MHz): δH 1.01 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 2.10 (q, J=13.8, 16.89 Hz, 2H, –CH₂), 2.84 (s, 3H, –CH₃), 6.87 (s, 1H, –CH), 7.30–7.36 (m, 2H, Ar-H), 7.51 (s, 1H, Ar-H), 7.59 (s, 1H, Ar-H), 7.71 (m, 1H, Ar-H), 7.73 (s, 1H, Ar-H), 8.19 (s, 1H, NH), 11.15 (s, 1H, NH) ppm. ¹³C NMR (75 MHz, CDCl₃): δ 162.87, 142.13, 130.76, 126.94, 123.31, 112.23, 60.89, 58.51, 14.83, 12.72. MS m/z (ESI): 311 [M+H⁺].

III. Conclusion
In conclusion we have developed an environmentally benign protocol for the synthesis of 1,2,4-triazolo[5,1-b] quinolin-8(4H)-one derivatives by using 3-amino-1,2,4-triazole, benzaldehydes and dimedone in the presence of 5mmol% Boric acid as a catalyst. The catalyst was found to catalyze reaction at room temperature. The advantages of this procedure are short reaction time, low cost, high reaction yield, need of no chromatographic separation step for water soluble catalyst.

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