TRICHLOROTRIAZINE PROMOTED MICROWAVE INDUCED THREE-COMPONENT SYNTHESIS OF QUINAZOLINONES IN AQUEOUS MEDIA

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Abstract - A series of quinazolin-4(1H)-ones have been synthesized in excellent yields and short reaction time by one-pot reaction of isatoic anhydride, ammonium acetate and aldehydes under microwave irradiation in water. The reaction was efficiently promoted by 0.09 g trichlorotriazine (TCT).

Keywords - quinazolinone; TCT; isatoic anhydride; microwave

I. INTRODUCTION

Dihydroquinazoline derivatives are an important class of fused heterocyclic that display a wide range of biological, pharmacological, and medicinal properties involving anticonvulsant, sedative, tranquilizer, antimicrobial, anesthetic, antitumor, antiviral, antihypertensive, anti-inflammatory, antibacterial, antipyretic, analgesic, antipyretic, diuretic, antihistamine, antidepressant, muscle relaxant and vasodilating activities [1, 2].

Several methods have been reported for synthesis of quinazolinone and aryl-substituted quinazolinone compounds including condensation of anthranilamide with an aldehyde or ketone using p-toluenesulfonic acid as a catalyst [3], desulfurization of 2-thioxo-4(3H)-quinazolinones [4], one-step conversion of 2-nitrobenzamides to 2, 3-dihydroquinazolin-4(1H)-ones [5], reaction of isatoic anhydride with Schiff bases [6], condensation of anthranilamide with benzyl [7], two-step synthesis starting from isatoic anhydride and amines, followed by annulation with ketones [8], reductive cyclization of o-nitrobenzamides and orthoformate, aldehydes, or ketones with the aid of a low-valent titanium reagent [9, 10] and reduction of the azide functionality [11].

In 2005, Salehi and Dabiri [12, 13] reported a more attractive and atom-efficient strategy for the preparation of 2, 3-dihydroquinazolin-4(1H)-ones, which involves a one-pot three-component reaction of isatoic anhydride, aldehydes, and amines. Nowadays, three-component condensation of an isatoic anhydride, a primary amine, and an aromatic aldehyde for the synthesis of quinazolinones has been widely described under a variety of catalysts such as [bmim] BF₄ [14], p-TsOH [15], silica sulfuric acid [13], Al(H₂PO₄)₃ [16], KAl(SO₄)₂·12H₂O [13], montmorillonite K-10 [17], zinc perfluoroocatanaote [18], gallium trflate [19], and Amberlyst-15/microwave [20], ethylenediamine diacete [21], I₂ [22], Al₂O₃, and Fe₃O₄ nanoparticle [23, 24], p-toluenesulfonic acid–paraformaldehyde copolymer [25], MCM-41-SO₃H [26], silica-bonded N-propylsulfamic acid [27], and copper benzensulfonate [28]. However, these methods suffer from disadvantage, such as strongly acid conditions, long reaction time, high temperature, poor selectivity, expensive reagent, toxicity, and need for excessive amounts of reagents. To avoid using strong acids or bases and other corrosive media and replacing hazardous or expensive reactants and reagents by safer and economic ones, it is desirable to develop a green and efficient protocol for the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones.
RESULTS AND DISCUSSION
As part of our ongoing interest for the development of efficient and environmentally friendly procedures for the synthesis of heterocyclic and pharmaceutical compounds, we wish to report the first TCT promoted synthesis of some derivatives of quinazolinones under microwave irradiation (Scheme 1).

In an initial endeavor, 1a, isotonic anhydride 2 and ammonium acetate were irradiated by microwave in the presence of optimized quantity of TCT (0.09 g) in 10 mL H2O. After 1 minute only 97% of product was obtained. In order to investigate the scope and generality of this promoter, various aldehydes were used in this reaction. The results are summarized in Table 1. Initially, in the proposed mechanism for this reaction, it seems TCT act as a promoter to produce a Lewis acid activating carbonyl of ester and then ammonia can attack to intermediate II, followed by departure of CO2, compound III was formed. Amine substituent in compound III by nucleophilic attack to active aldehyde was converted to imine intermediate V. Finally, with an intramolecular reaction, product 3 was observed.

2-(3-nitrophenyl)-2,3-dihydroquinazolin-4-(1H)-one (3a): Yield: 97%; m.p. 213-215 °C; Anal. Calcd. For C14H11N3O3: C, 62.45; H, 4.12; N, 15.61; Found: C, 62.36; H, 4.19; N, 15.52; IR (KBr, cm⁻¹): 3358 (-NH stretching of secondary amine), 3192 (-NH stretching of secondary amine), 3067, 2918, 1645 (-C=O stretching of –CONH group), 1614, 1500 (-C=O stretching of aromatic ring), 1389, 1327; 1HNMR (500 MHz, DMSO-d6, δ ppm): 6.10 (s, 1H, C-H chiral center), 6.67 (t, 1H, J = 7.4 Hz, aromatic), 6.72 (d, 1H, J = 8.1 Hz, aromatic), 7.21 (d, 1H, J = 7.0 Hz, aromatic), 7.34-7.37 (m, 2H, aromatic), 7.43-7.46 (m, 1H, aromatic), 7.62 (d, 1H, J = 7.0 Hz, aromatic), 8.16 (s, 1H, -NH, D2O exchangeable). 13CNMR (125MHz, DMSO-d6, δ ppm): 64.14 (carbon chiral), 115.02, 115.13, 117.92, 127.84, 127.94, 129.20, 130.77, 132.31, 133.91, 138.31, 148.11, 164.10 (C=O).

2-(naphtyl-1-yl)-2,3-dihydroquinazolin-4-(1H)-one (3c): Yield: 97%; m.p. 111-113 °C; Anal. Calcd. For C18H14N2O: C, 78.81; H, 5.14; N, 10.21; Found: C, 78.74; H, 5.20; N, 10.14; IR (KBr, cm⁻¹): 3312 (-NH stretching of secondary amine), 3187 (-NH stretching of secondary amine), 3045, 2939, 1656 (-C=O stretching of –CONH group), 1605, 1512 (-C=O stretching of aromatic ring), 1370, 1321; 1HNMR (500 MHz, DMSO-d6, δ ppm): 5.89 (s, 1H, C-H chiral center), 6.63 (t, 1H, J = 7.4 Hz, aromatic), 6.72 (d, 1H, J = 8.1 Hz, aromatic), 7.13 (s, 1H, -NH, D2O exchangeable), 7.21 (d, 1H, J = 7.0 Hz, aromatic), 7.48 – 7.50 (m, 2H, aromatic), 7.58 (d, 1H, J = 7.1 Hz, aromatic), 7.64 (d, 1H, J = 8.6 Hz, aromatic), 7.87- 7.97 (m, 3H, aromatic), 8.30 (s, 1H, -NH, D2O exchangeable). 13CNMR (125MHz, DMSO-d6, δ ppm): 63.75 (carbon chiral), 116.43, 116.94, 118.98, 123.57, 124.04, 125.05, 127.50, 129.55, 130.33, 130.65, 134.91, 135.66, 136.32, 137.01, 138.48, 146.22, 165.23 (C=O).

2-(1,4-phenylen)bis(2,3-dihydroquinazolin-4-(1H)-one (3d): Yield: 99%; m.p. 122-113 °C; Anal. Calcd. For C22H18N4O2: C, 71.34; H, 4.90; N, 15.13; Found: C, 71.39; H, 4.89; N, 15.09; IR (KBr, cm⁻¹): 3747 (-NH stretching of secondary amine), 3446 (-NH stretching of secondary amine), 3068, 2926, 1653 (-C=O stretching of –CONH group).
Table 1. Microwave assisted TCT catalyzed synthesis of quinazolinones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time / min</th>
<th>Yield / %</th>
<th>Mp/ °C</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-nitrobenzaldehyde</td>
<td>3a</td>
<td>1</td>
<td>97</td>
<td>190-192/195-196</td>
<td>[17,26]</td>
</tr>
<tr>
<td>2</td>
<td>2-Chlorobenzaldehyde</td>
<td>3b</td>
<td>3</td>
<td>95</td>
<td>205-206/ 208-210</td>
<td>[26]</td>
</tr>
<tr>
<td>3</td>
<td>2-naphtylcarbaldehyde</td>
<td>3c</td>
<td>2</td>
<td>97</td>
<td>111-113/ -</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Theophthaldehyde</td>
<td>3d</td>
<td>3</td>
<td>99</td>
<td>122-123/ -</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>4-bromobenzaldehyde</td>
<td>3e</td>
<td>2</td>
<td>96</td>
<td>171-173/ -</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>4-Chlorobenzaldehyde</td>
<td>3f</td>
<td>1</td>
<td>95</td>
<td>200-202/ 206-207</td>
<td>[17, 23, 26]</td>
</tr>
<tr>
<td>7</td>
<td>4-methylbenzaldehyde</td>
<td>3g</td>
<td>5</td>
<td>94</td>
<td>217-218-224-226</td>
<td>[17,23,26]</td>
</tr>
<tr>
<td>8</td>
<td>4-methoxybenzaldehyde</td>
<td>3h</td>
<td>5</td>
<td>92</td>
<td>184-185/ 184-186</td>
<td>[17,23,26]</td>
</tr>
<tr>
<td>9</td>
<td>4-hydroxybenzaldehyde</td>
<td>3i</td>
<td>4</td>
<td>95</td>
<td>201-202/ -</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>N,N-dimethylaminobenzaldehyde</td>
<td>3j</td>
<td>4</td>
<td>94</td>
<td>209-210/ 210-212</td>
<td>[17,23,26]</td>
</tr>
<tr>
<td>11</td>
<td>Benzaldehyde</td>
<td>3k</td>
<td>4</td>
<td>91</td>
<td>212-214-217-222</td>
<td>[17, 23, 26]</td>
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<tr>
<td>12</td>
<td>Furfural</td>
<td>3l</td>
<td>3</td>
<td>96</td>
<td>219-220/ 221-222</td>
<td>-</td>
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<tr>
<td>13</td>
<td>2-pyridincarbaldehyde</td>
<td>3m</td>
<td>2</td>
<td>98</td>
<td>271-272/ -</td>
<td>-</td>
</tr>
</tbody>
</table>

a. Entries 1, 2, 6-8 and 11 are known and their spectra and physical data have been reported in literature.
REFERENCES

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ACKNOWLEDGMENT

Finally, we develop an efficient and convenient procedure for the synthesis of quinazolinones through three component synthesis of aldehydes, isonitric anhydride and ammonium acetate. This procedure offer advantages such as reduced reaction time, mild reaction condition, productivity and higher yield and ease of execution.

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REFERENCES