Microwave-assisted synthesis of 3-substituted coumarins using ZrOCl$_2$·8H$_2$O as an effective catalyst

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Abstract

An efficient route for the synthesis of 3-substituted coumarins via Knoevenagel condensation using ZrOCl$_2$·8H$_2$O (10 mol %) as the catalyst under microwave heating and solvent-free conditions is described. This procedure offers several advantages including low loading of catalyst, high yields, clean reaction, short reaction time and use of various substrates, which make it a useful and attractive strategy for the synthesis of 3-substituted coumarins.

Keywords: 3-Substituted coumarins; ZrOCl$_2$·8H$_2$O; Microwave heating

1. Introduction

Coumarins and their derivatives are very important organic compounds. They are the structural unit of several natural products [1]. Their applications range from pharmaceuticals [2], optical brighteners [3] and laser dyes [4]. Also coumarins and functionalized coumarins have shown activity as antimicrobials and chemotherapeutics [5]. These properties have made coumarins into interesting targets for organic chemists.

Various methods are known for the synthesis of substituted coumarins in the literature including the Pechmann [6a], Perkin [6b], Knoevenagel [6c], Claisen [6d], Reformatsky [6e] and Wittig reactions [6f]. Coumarins have been synthesized by the Kostanecki–Robinson reaction of o-hydroxyarylalkyl ketones with acid anhydrides, which proceeds through an ester enolate intermediate [7]. Disadvantages of this method include the formation of chromone byproducts and variable yields. One of the most widely used methods is the Pechmann reaction, which involves the condensation of a phenol with a β-ketoester. The major drawback of this protocol stems from its requirement for
strong acid (e.g., concentrated sulfuric acid) in large excess and at high temperature with obvious limitations on the scope of this reaction. Some of the recent efficient methods utilize several heterogenous as well as transition metal catalysis [8], solid phase synthesis [9] and ionic liquids [10]. Most of the procedures suffer from harsh reaction conditions (such as the use of stoichiometric amounts of mineral, Lewis acids or toxic reagents, often under high temperatures and longer reactions times), poor substituents tolerance, and low yields [11], thus it is clearly evident that the need for the development of new and flexible protocols is required.

On the other hand in recent years the concept of speeding up the synthetic transformations by microwave activation has created a lot of interest in organic synthesis [12] The coupling of microwave heating with solid phase in solvent-free conditions catalysts chemical processes with special attributes such as enhanced reaction rate, ease of work-up and high yields.

As part of our research, aiming to explore potential ability of microwave as an energy source for organic synthesis under solvent-free conditions [13], herein we report the ZrOCl$_2$.8H$_2$O catalyzed solvent-free one-pot protocol for the synthesis of 3-substituted coumarins under microwave heating (Scheme 1).

![Scheme 1. ZrOCl$_2$.8H$_2$O catalyzed synthesis of 3-substituted coumarins under microwave heating.](image)

The using of zirconium salts in organic transformation such as conversion of aromatic, aliphatic nitro compounds to primary amines [14a] hydrodechlorination of dichlorodifluoromethane [14b] oxidation of alcohols [14c] Michael reactions [14e-14f], and acylation reactions [14g] has been recently reported. ZrOCl$_2$.8H$_2$O is relatively nontoxic, inexpensive and insensitive to air.

2. Experimental

2.1. Apparatus and characterization
The compounds gave all satisfactory spectroscopic data. A Bruker (DRX-500 Avanes) NMR was used to record the $^1$H-NMR, $^{13}$C-NMR spectra. All NMR spectra were determined in CDCl$_3$ at ambient temperature. Melting points were determined on a Buchi B540 apparatus. GC-MS (EI), 70ev, HP6890 Coulumn: HP-5 (30m x 0.25mm x0.2uml MSD: HP5793) was used to record the mass spectra.

2.2. General procedure

To an equimolar mixture of the 2-hydroxybenzaldehyde and diethylmalonate, ZrOCl$_2$.8H$_2$O (10 mol %) was added then the mixture was heating in a single mode microwave oven for 6 minute. After cooling, the residue was subjected to column chromatography (EtOAc/hexane; 1:3) on silica gel to obtain pure products.

2.3. Selected spectroscopic data: Table 2, (1a), $^1$HNMR (CDCl$_3$); $\delta$(ppm): 1.45(t, 3H), 4.46(q, 2H), 7.38(m, 2H), 7.69(m, 2H), 8.56(s, 1H). $^{13}$CNMR (CDCl$_3$); $\delta$(ppm): 14.62, 62.37, 117.22, 118.36, 118.99, 125.18, 129.84, 134.63, 148.78, 155.65, 157.00, 163.51. MS (EI): 218(M$^+$, 35), 173(98), 146(100), 118(20), 89(33). Table 2, (1c), $^1$HNMR (CDCl$_3$); $\delta$(ppm): 7.38 (t, 1H), 7.44 (d, 1H), 7.51 (t, 2H), 7.62-7.70 (m, 3H), 7.92(d, 2H), 8.10 (s, 1H). $^{13}$CNMR (CDCl$_3$); $\delta$(ppm): 117.32, 118.66, 125.31, 127.65, 129.96, 133.91, 134.11, 136.77, 145.51, 155.25, 158.68, 191.94. MS (EI): 250(M$^+$, 98), 221(71), 173(34), 105(100), 77(86). Table 2, Solid (1d), $^1$HNMR (CDCl$_3$); $\delta$(ppm): 7.45(t, 2H), 7.67(d, 1H), 7.77 (t, 1H), 8.32(s, 1H). $^{13}$CNMR (CDCl$_3$); $\delta$(ppm): 103.77, 113.96, 115.66, 119.21, 120.80, 125.30, 127.67, 129.02, 130.05, 134.25, 136.59, 144.87, 146.10, 147.65, 158.36, 192.18. MS (EI): 280(M$^+$, 80), 265(20), 251(35), 105(100), 77(70). Table 2, (3a), $^1$HNMR (CDCl$_3$); $\delta$(ppm): 1.45(t, 3H), 4.46(q, 2H), 7.30(s, 1H), 7.76 (d, 1H), 7.78 (d, 1H), 8.47 (s, 1H). $^{13}$CNMR (CDCl$_3$); $\delta$(ppm): 14.63, 62.67, 117.79, 118.98, 119.76, 119.90, 131.95, 137.38, 147.49, 154.38, 156.43, 163.09. MS (EI): 296(M$^+$, 45), 253(76), 224(100), 196(25), 167(25), 88(36), 55(47).
3. Results and discussion

Among these to study efficiency of ZrOCl$_2$.8H$_2$O for Knoevenagel condensation, the reaction of salicylaldehyde with diethylmalonate was selected as model. First experiments focused on comparing ZrOCl$_2$.8H$_2$O with other catalysts under different conditions. The results were summarized in the Table 1. As shown in Table 1, the use of ZrOCl$_2$.8H$_2$O, as a catalyst for solventless reactions under microwave heating, offers a convenient, environmentally friendly alternative to conventional reactions (Table 1, entry 3). Clearly, the reaction time by microwave heating has been reduced 10 times with higher yield than conventional heating (86% versus 55%, Table 1 entry 3, 5). Since the product of interest is not covalently bound to the solid support, monitoring of the reactions and analysis can be accomplished by using standard methods (thin layer chromatography, column chromatography $^1$H NMR, etc.). Finally, the products are isolated by column chromatography, eliminating the need for a cleavage step that is required in solid phase synthesis.

On the optimization of the amount of ZrOCl$_2$.8H$_2$O, we found that a 10 mol% amount ZrOCl$_2$.8H$_2$O could effectively catalyze the reaction. With inclusion of 5 mol % of ZrOCl$_2$.8H$_2$O the reaction took longer time. Using more ZrOCl$_2$.8H$_2$O (20 mol %) has less effect on the yield and time of the reaction (89 % versus 86 %). This reaction has been already performed using the piperidine (Table 1, entry 4) [15]. The results show that ZrOCl$_2$.8H$_2$O is more efficient than other catalysis.

Table 1 The reaction of salicylaldehyde with diethylmalonate with different conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Temperature(°C)</th>
<th>Time(min)</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuSO$_4$</td>
<td>MW</td>
<td>120</td>
<td>6</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>SiO$_2$/KOH</td>
<td>MW</td>
<td>120</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>ZrOCl$_2$</td>
<td>MW</td>
<td>120</td>
<td>6</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>piperidine</td>
<td>MW/EtOH</td>
<td>129</td>
<td>10</td>
<td>89</td>
</tr>
</tbody>
</table>
To generalize this methodology, we subjected a series of ethyl acetate derivatives (e.g., COOEt, COOMe, COPh, and CN) with a variety of 2-hydroxybenzaldehydes to obtain the corresponding substituted coumarins. The results are summarized in the Table 2.

As it is shown in Table 2 the reaction was found to be adaptable to a variety of substrates and in general was high the yields (60-92%). Short reaction time (6 min) and a lower amount of ZrOCl$_2$.8H$_2$O (10 mol%) were observed.

Table. 2 ZrOCl$_2$.8H$_2$O (10 mol %) catalyzed synthesis of 3-substituted coumarins under solvent-free conditions by microwave heating.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-hydroxybenzaldehyde</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
<th>mp (ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R= COOEt</td>
<td>1a</td>
<td>86</td>
<td>93-94</td>
</tr>
<tr>
<td></td>
<td>R= COOMe</td>
<td>1b</td>
<td>84</td>
<td>108-109</td>
</tr>
<tr>
<td></td>
<td>R= COPh</td>
<td>1c</td>
<td>90</td>
<td>148-149</td>
</tr>
<tr>
<td></td>
<td>R= CN</td>
<td>1d</td>
<td>62</td>
<td>184-185</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R= COOEt</td>
<td>2a</td>
<td>88</td>
<td>88-89</td>
</tr>
<tr>
<td></td>
<td>R= COPh</td>
<td>2b</td>
<td>92</td>
<td>146-147</td>
</tr>
<tr>
<td></td>
<td>R= CN</td>
<td>2c</td>
<td>60</td>
<td>225-226</td>
</tr>
</tbody>
</table>
All the coumarins derivatives are well-known in the literatures and were identified by comparison of their physical and spectral data (GC-MS, $^1$HNMR and $^{13}$CNMR) [16].

4. Conclusions

In conclusion, the ZrOCl$_2$.8H$_2$O shows high catalytic activities for the synthesis 3-substituted coumarins via Knoevenagel condensation under solvent-free conditions by microwave heating. This procedure offers several advantages including low loading of catalyst, high yields, clean reaction, and use variety of substrates, which make it a useful and attractive strategy for the synthesis of 3-substituted coumarins. In addition, a very easy workup has been realized that does not require organic solvents. The generality of the method has been demonstrated by the successful conversion of twelve substrates into 3-substituted coumarins in good yields. This methodology could serve as a valuable alternative to known methods.

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References


