

Microwave-Assisted Synthesis of 3-Substituted Coumarins Using $ZrOCl_2 \cdot 8H_2O$ as an Effective Catalyst

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Abstract. An efficient route for the synthesis of 3-substituted coumarins via Knoevenagel condensation, using $ZrOCl_2 \cdot 8H_2O$ (10 mol %) as the catalyst under microwave heating and solvent-free conditions, is described. This procedure offers several advantages, including the low loading of catalysts, high yields, clean reactions, short reaction times and the use of various substrates, which make it a useful and attractive strategy for the synthesis of 3-substituted coumarins.

Keywords: 3-substituted coumarins; $ZrOCl_2 \cdot 8H_2O$; Microwave heating.

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 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]. The disadvantages of this method include the formation of chromone by-products 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 a large excess and at high temperature with obvious

limitations on the scope of this reaction. Some of the recent efficient methods utilize several heterogeneous as well as transition, metal catalyses [8], solid phase synthesis [9] and ionic liquids [10]. Most of the procedures suffer from harsh reaction conditions (such as the use of stoichiometric amount of minerals, Lewis acids or toxic reagents, often under high temperatures and with longer reaction times), poor substituents tolerance and low yields [11]. Thus, it is clearly evident that development of new and flexible protocols is required.

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

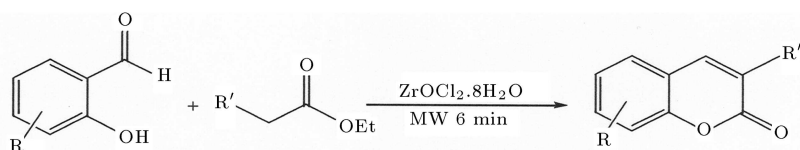
Part of our research is aiming to explore the potential ability of the microwave as an energy source for organic synthesis under solvent-free conditions [13]. Herein, we report the $ZrOCl_2 \cdot 8H_2O$ catalyzed solvent-free one-pot protocol for the synthesis of 3-substituted coumarins under microwave heating (Scheme 1).

The use of zirconium salts in organic transformation, such as the 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.

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Scheme 1. $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ catalyzed synthesis of 3-substituted coumarins under microwave heating.

$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ is relatively nontoxic, inexpensive and insensitive to air.

EXPERIMENTAL

Apparatus and Characterization

The compounds gave all satisfactory spectroscopic data. A Bruker (DRX-500 Avanes) NMR was used to record the ^1H -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), 70 ev, HP6890 Column: HP-5 (30m \times 0.25mm \times 0.2um) MSD: HP5793) were used to record the mass spectra.

General Procedure

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

Selected Spectroscopic Data

Table 2, (**1a**), ^1H NMR (CDCl_3); δ (ppm): 1.45(t, 3H), 4.46(q, 2H), 7.38(m, 2H), 7.69(m, 2H), 8.56(s, 1H). ^{13}C NMR (CDCl_3); δ (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**), ^1H NMR (CDCl_3); δ (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}C NMR (CDCl_3); δ (ppm): 117.32, 118.66, 125.31, 127.65, 128.97, 129.56, 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**), ^1H NMR (CDCl_3); δ (ppm): 7.45(t, 2H), 7.67(d, 1H), 7.77 (t, 1H), 8.32(s, 1H). ^{13}C NMR (CDCl_3); δ (ppm): 103.77, 113.96, 117.56, 117.89, 129.15, 129.73, 136.00, 152.29, 155.02, 156.88. MS (EI): 171(M^+ , 100), 143(97), 115(37), 88(21), 63(15). Table 2, (**2b**), ^1H NMR (CDCl_3); δ (ppm): 4.03(s, 3H), 7.23 (t, 2H), 7.30 (d, 1H), 7.51 (t, 2H), 7.65 (t, 1H), 7.91(d, 2H), 8.10 (s, 1H). ^{13}C NMR (CDCl_3); δ (ppm): 56.78, 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**), ^1H NMR (CDCl_3); δ (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}C NMR (CDCl_3); δ (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).

RESULTS AND DISCUSSION

In order to study the efficiency of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ for Knoevenagel condensation, the reaction of salicylaldehyde with diethylmalonate was selected as the model. First, the experiments focused on comparing $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ with other catalysts under different conditions. The results were summarized in Table 1. As shown in Table 1, the use of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$, 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 a higher yield than by 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 ^1H NMR, etc.). Finally, the products are isolated by column chromatography, eliminating the need for a cleavage step that is required in a solid phase synthesis.

On the optimization of the amount of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$, we found that a 10 mol% amount $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ could effectively catalyze the reaction. With the inclusion of 5 mol % of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$, the reaction took longer. Using more $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ (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 $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ is more efficient than other catalyses.

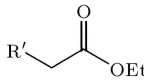
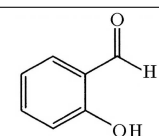
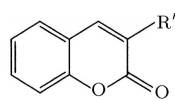
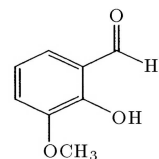
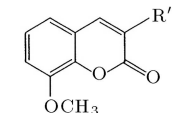
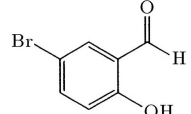
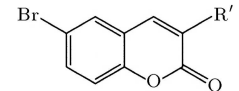
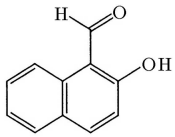
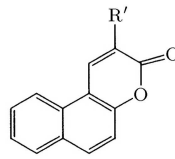
To generalize this methodology, we subjected a series of ethyl acetate derivatives (e.g. COOEt, COOMe, CPh and CN) with a variety of 2-hydroxybenzaldehydes in order to obtain the corresponding substituted coumarins. The results are summarized in Table 2.

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

| Entry | Catalyst | Conditions | Temperature (°C) | Time (min) | Yield% |
|-------|-----------------------|----------------------|------------------|------------|-------------|
| 1 | CuSO ₄ | MW | 120 ^a | 6 | No reaction |
| 2 | SiO ₂ /KOH | MW | 120 ^a | 6 | 45 |
| 3 | ZrOCl ₂ | MW | 120 ^a | 6 | 86 |
| 4 | piperidine | MW/EtOH | 129 | 10 | 89 |
| 5 | ZrOCl ₂ | Conventional heating | 90 ^a | 60 | 55 |
| 6 | ZrOCl ₂ | CH ₃ CN | 80 | 480 | 20 |
| 7 | ZrOCl ₂ | DMSO | 120 | 480 | No reaction |

a: Solvent-free.

Table 2. ZrOCl₂.8H₂O (10 mol %) catalyzed the synthesis of 3-substituted coumarins under solvent-free conditions by microwave heating.

| Entry | 2-hydroxybenzaldehyde |  | Product | Yield (%) ^a | mp (°C) |
|-------|---|--|--|------------------------|---------|
| 1 |  | $R' = \text{COOEt}$ $R' = \text{COOMe}$ $R' = \text{COPh}$ $R' = \text{CN}$ |  | 86 | 93-94 |
| | | | 1a | 84 | 108-109 |
| | | | 1b | 90 | 148-149 |
| | | | 1c | 62 | 184-185 |
| 2 |  | $R' = \text{COOEt}$ $R' = \text{COPh}$ $R' = \text{CN}$ |  | 88 | 88-89 |
| | | | 2a | 92 | 146-147 |
| | | | 2b | 60 | 225-226 |
| 3 |  | $R' = \text{COOEt}$ $R' = \text{COPh}$ $R' = \text{CN}$ |  | 76 | 180-181 |
| | | | 3a | 84 | 176-177 |
| | | | 3b | 66 | 200-201 |
| 4 |  | $R' = \text{COOEt}$ $R' = \text{COPh}$ |  | 69 | 117-118 |
| | | | 4a | 79 | 216-217 |
| | | | 4b | | |

a: All yields refer to isolated products.

As shown in Table 2, the reaction was found to be adaptable to a variety of substrates and, in general, the yields were high (60-92%). A short reaction time (6 min) and a lower amount of $ZrOCl_2 \cdot 8H_2O$ (10 mol%) were observed.

All the coumarins derivatives are well-known in the literature and were identified by a comparison of their physical and spectral data (GC-MS, 1H NMR and ^{13}C NMR) [16].

CONCLUSIONS

In conclusion, the $ZrOCl_2 \cdot 8H_2O$ 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 the low loading of catalysts, high yields, clean reactions, and the use of a variety of substrates, which makes it a useful and attractive strategy for the synthesis of 3-substituted coumarins. In addition, a very easy work-up 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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