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Microwave assisted synthesis of ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate via manganese(III) acetate mediated radical cyclization reaction

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Abstract

"Ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate" is dihydro-furan-fused monocyclic heterocycles containing dihydrofurocoumarin framework. Compounds that include these core structures are especially important for drug discovery.

Manganese(III) acetate has been used as an efficient oxidizing agent for the preparation of "ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate" by the multi-steps reaction of ethyl 3,3-bis(4-fluorophenyl)acrylate and 4-hydroxycoumarin under microwave irradiation to perform faster heating times, significantly reduce reaction times, and the efficient solubilization of manganese(III) acetate in acetic acid. The cyclization reaction was achieved using reactivity of the carbonyl group within the molecule.

Keywords

Dihydrofuran, manganese(III) acetate, microwave irradiation, radical cyclization reaction.

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INTRODUCTION

Heterocycles are generally important in the field of medicinal chemistry for drug discovery. Drugs containing heterocycles are used in a number of therapies, including those for cancer, ulcer, metabolic and cardiovascular diseases, infections, and central nervous system (CNS)-related illnesses. Furan, thiophene, and pyrrole are among the most popular five-membered heterocycles with a single heteroatom and are of great importance for the discovery of novel drugs (Riddell, 1980; Li, 2013).

The salts of transition metal (Mn^{3+}, Co^{3+}, Cu^{2+}, Ce^{4+}) that are capable of transferring single electrons are known to produce α-carbon radicals with enolizable functional groups, which can generate new carbon-carbon bonds when added to unsaturated systems (Iqbal *et al.*, 1994; Ozgur *et al.*, 2019; Akpinar *et al.*, 2018; Aslan *et al.*, 2014; Yilmaz *et al.*, 2008). Manganese(III) acetate, cerium(IV) ammonium nitrate are the most commonly-used types of these metal salts (Bar *et al.*, 2001; Kajikawa *et al.*, 2001).

Reaction mixtures that include manganese(III) acetate are known as suitable candidates for microwave irradiation, despite being considered in a limited number of publications (Mu *et al.*, 2005). Microwave irradiation could potentially facilitate the rapid heating, efficient solubilization, and significantly reduce the reaction time of $Mn(OAc)_3$ in acetic acid (Curti *et al.*, 2009). Consequently, it has widely been used as a controllable, yet powerful method of heating organic reactions. Microwave reactions typically result in higher yields, better selectivities, and shorter reaction times (Larhed and Hallberg, 2001; Larhed *et al.*, 2002; Wathey, 2002; Kappe, 2002; Kappe and Stadler, 2005; Eycken, 2006; Kappe *et al.*, 2009).

MATERIALS AND METHODS

Triethyl phosphonoacetate **(1)**, bis (4-fluorophenyl) methanone **(2)** and 4-hydroxycoumarin **(4)** were obtained from Sigma Aldrich. Because the purity of these compounds was more than % 99, no other purification step was applied.

Synthesis of starting material: "Ethyl 3,3-bis(4-fluorophenyl) acrylate (3)"

As shown in Figure 1, conjugated ester **(3)** was synthesized by using triethyl phosphonoacetate **(1)** and bis (4-fluorophenyl) methanone **(2)** in tetrahydrofuran (THF) and sodium hydride (NaH) (Pinna *et al.*, 2003; Burgaz *et al.*, 2011).

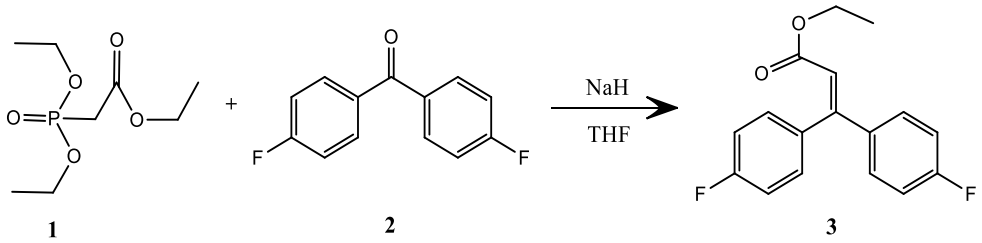

Figure 1: General mechanism for the synthesis of ethyl 3, 3-bis (4-fluorophenyl) acrylate.

A solution of triethyl phosphonoacetate (120 mmol, 21 mL) in THF (50 mL) was added dropwise to a solution of NaH (120 mmol, 60% dispersion in mineral oil, 4.8 g) in THF (200 mL) within ice bath. Half an hour later, the suitable ketone (100 mmol) was added to the reaction mixture and was stirred for 2-3 days at room temperature. When the reaction was finished, THF was subjected to decreased pressure and vaporized. The remainder was extracted with diethyl ether. Afterwards, the organic layer was dried by sodium sulfate and vaporized. The crude product was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (5:1).

Synthesis of "ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate"

General mechanism for the synthesis of ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate is shown in Figure 2.

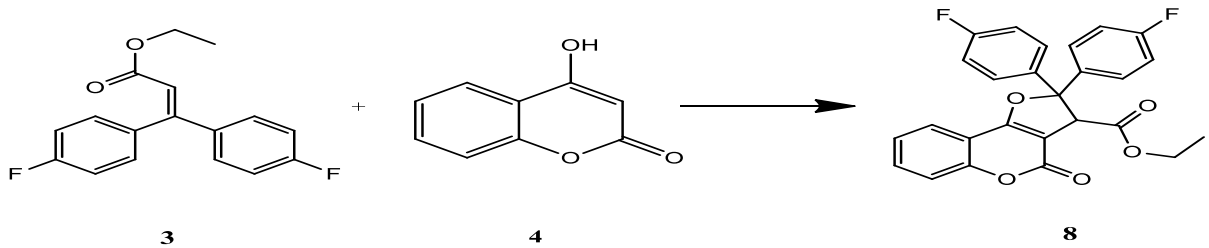

Figure 2: General mechanism for the synthesis of ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate.

4-hydroxycoumarin **(4)** (1 mmol, 0.163 g) and subsequently ethyl 3,3-bis(4-fluorophenyl) acrylate **(3)** (0.5 mmol, 0.145 g) were added to a test tube containing manganese(III) acetate dihydrate (3 mmol, 0.804 g) and mixed well. Acetic acid was added into the tube and the mixture was poured into a microwave reaction vial with a magnet inside the vessel for mechanical stirring. The vial was placed inside the microwave machine.

Optimization of the reaction

In order to maximize performance, optimization was carried out. To produce the higher amount of the product with the minimum waste, the percentage yield is

extremely remarkable and is useful as an indicator that the strategy is productive and accurate. Therefore, various factors such as temperature, time, pressure and concentrations were arranged to obtain the highest-yield of the product. Finally, the microwave machine was adjusted at 80˚C for 5 minutes. After the reaction was completed, water was added and extraction was done with chloroform. The organic layer was dried over sodium sulfate and then evaporated. The product was purified by silica gel column chromatography eluting with hexane/ethyl acetate (3:1) to give the product ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate **(8)** (0.124 g, 55 %).

Mechanism of reaction

In the synthesis of the product **(8)**, the very early reaction is the generation of the radical form of 4-hydroxycoumarin **(5)** due to the addition of MAH (Figure 3). The unpaired electrons positioned on secondary radical 4-hydroxycoumarin **(5)** make the compound highly reactive. Thus, the π-bond of 2,3-diene chain belonging to ethyl 3,3-bis(4-fluorophenyl)acrylate **(3)** is captured by the radical during the addition of acetic acid, being broken down forming benzyl radical (because benzyl radical is more stable than secondary radical). Then, the produced intermediate **(6)** is converted to the enol form **(7)** which subsequently undergoes intramolecular reaction with the attack of the oxygen atom on the enol group to the carbocation to form the cyclized product **(8)** (Figure 4).

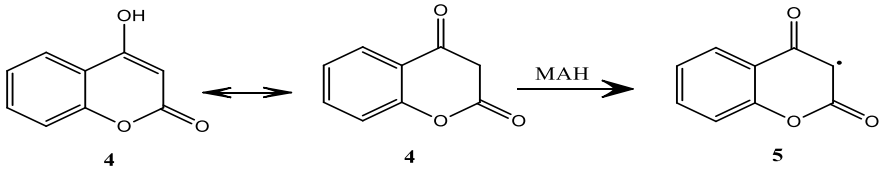

Figure 3: Mechanism of reaction for the radical generation of 4-hydroxycoumarin.

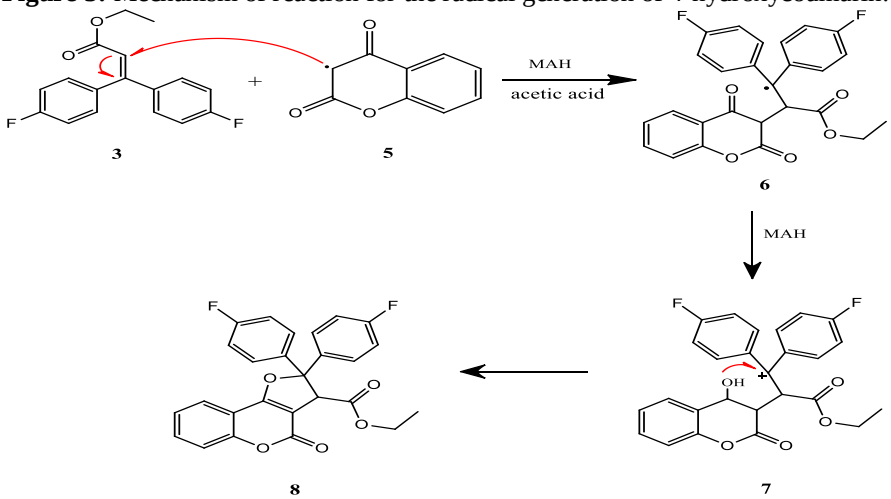

Figure 4: Mechanism of reaction for the synthesis of ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate.

RESULTS AND DISCUSSION

In this study, free radical cyclization reaction method was developed under the assistance of microwave irradiation for the synthesis of ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate **(8)**. Microwave-assisted heating results in include faster heating times, significantly reduced reaction times, and the efficient solubilization of utilized reagents. Therefore, the method has found a number of different technological applications in drug discovery and medicinal chemistry.

Ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate was synthesized successfully. ^{1}H-NMR and ^{13}C-NMR results show that protons and carbon atoms involved in this compound are completely comparable to the structure of product that was expected according to the mechanism of reaction.

Ethyl 3,3-bis(4-fluorophenyl)acrylate (3) : ^{1}H-NMR (CDCl3), δ (ppm): 1.15 (3H, t, J = 7.2 Hz, CH_3), 4.07 (2H, q, J = 7.2 Hz, CH_2), 6.30 (1H, s, alkene H), 7.00- 7.05 (2H, m, ArH), 7.07- 7.10 (2H, m, ArH), 7.16- 7.19 (2H, m, ArH), 7.21- 7.28 (2H, m, ArH).

Ethyl 2,2-bis(4-fluorophenyl)-4-oxo-3,4-dihydro-2H-furo[3,2-c]chromene-3-carboxylate (8) : **^{1}H-NMR** (CDCl3), δ (ppm): 0.91 (3H, t, J = 7.2 Hz, CH_3), 3.68-3.82 (2H, m, CH_2), 4.96 (1H, t), 6.98 (2H, td, J = 8.4 and 2.0 Hz, ArH), 7.14 (2H, td, J = 8.4 and 2.0 Hz, ArH), 7.22-7.26 (2H, m, ArH), 7.37 (1H, td, J = 8.0 and 0.8 Hz, ArH), 7.42 (1H, d, J = 8.8 Hz, ArH), 7.64 (1H, td, J = 8.8 and 2.0 Hz, ArH), 7.69 (2H, m, ArH), 7.86 (1H, dd, J = 7.6 and 1.6 Hz, ArH). **^{13}C-NMR** ($CDCl_3$), δ (ppm): 13.86 (CH_3), 57.19, 61.92 (CH_2), 98.81, 101.88, 112.29, 115.02, 115.23, 115.88, 116.10, 117.53, 123.21, 124.49, 128.53, 129.01, 133.50, 135.33, 138.12, 155.68, 159.54, 161.62, 161.79, 164.10, 164.28 (C4), 166.10 (C=O), 168.30 (C=O).

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