

# Microwave-assisted TsOH/SiO<sub>2</sub>-catalyzed one-pot synthesis of novel fluoro-substituted coumarin hydrazones under solvent-free conditions



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## ABSTRACT

Sixteen novel fluoro-substituted coumarin hydrazones were synthesized from a series of ethyl 2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylates with supported acid catalyst under microwave-assisted one-pot and solvent free conditions. The structures of synthesized compounds were confirmed by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, HRMS and single crystal X-ray diffraction. Compared with the reported reaction conditions, the new method has the advantages of shorter reaction time, simple work-up procedure and environmental friendliness. The supported catalyst can be recovered easily and reused with little change in its activity.

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## 1. Introduction

Coumarin and its derivatives were reported to show a wide range of valuable biological activities in medicinal and pharmaceutical areas, such as antimicrobial, anti-inflammatory, anti-tubercular, platelet antiaggregator, anti-tumor, and antioxidant properties [1]. Moreover, several of them have excellent fluorescent properties because of their large Stokes shift. Therefore, they are used as dyes, sensors, and probes in the field of materials engineering [2]. The incorporation of fluorine-containing groups in the compounds often results in the improvement of their physiological properties [3]. Therefore, various fluoro-substituted coumarins have been recently synthesized [4]. The synthetic methods of fluoro-substituted coumarins mostly employ traditional techniques, thereby restricting the development of novel coumarin derivatives containing fluorine.

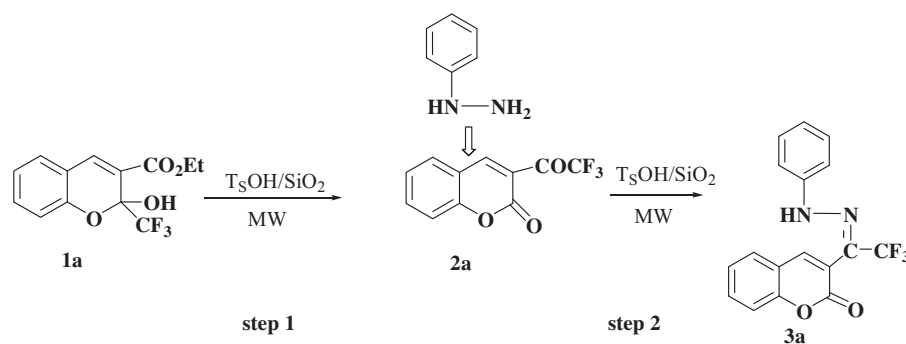
Among various coumarin derivatives, coumarin hydrazones have been under investigation in recent years, due to their usages as pharmaceuticals [5], fluorescence sensor [6], chemoreceptors [7] and precursors for coumarin pyrazoles [8]. For example, 3-(2,4-dinitrophenylhydrazonoethyl)coumarin could be acted as an intramolecular charge transfer (ICT) probe for the naked-eye

detection of a few biologically relevant anions in dimethylsulphoxide [7]. However, in contrast to 3-acetylcoumarin hydrazones which were abundantly prepared, few papers have been reported about the synthesis and application of 3-trifluoroacetylcoumarin hydrazones owing to the unavailable precursors, 3-trifluoroacetylcoumarins [9].

Recently, many new methodologies have been employed in every aspect of organic chemistry to make up for some deficiency of classical synthesis. For instance, the approach of microwave-assisted one-pot synthesis under solvent-free conditions has been preferred in scientific community because it is an efficient, rapid, and green synthetic method, and has been extensively exploited to synthesize many valuable organic compounds in the synthetic chemistry [10]. Furthermore, another protocol, the heterogenization of a homogeneous catalyst, also be commonly used to overcome the catalyst-product separation problem [11].

Li et al. [9] reported the successful synthesis of novel coumarin fluorescent dyes, which can be used as an optical chemosensor. However, the reported method has its drawbacks, such as longer reaction time, use of poisonous solvent (chlorobenzene), purification of the intermediates, and difficult separation of the catalyst from the products. Therefore, it is particularly important to find a novel strategy to synthesize fluoro-substituted coumarin hydrazones which have potentially unique biological activity due to the introduction of fluorine atoms.

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Scheme 1. Synthetic route of the compound **3a**.

In continuation of our work to develop the green synthesis of coumarin derivatives [12], here we report a novel, clean, and simple protocol for the synthesis of fluoro-substituted coumarin hydrazones through the reaction of fluoro-substituted coumarin esters with various hydrazines in the presence of TsOH/SiO<sub>2</sub> as a supported catalyst under solvent-free conditions.

## 2. Results and discussion

The reaction of compound **1a** with phenylhydrazine was chosen as a model reaction (Scheme 1). The reaction was carried out in two steps under solid acidic and microwave conditions. In step 1, fluoro-substituted coumarin ester **1a** was transformed into fluoro-substituted coumarin ketone **2a**. Then the ketone **2a**, which was not isolated from the mixture, directly reacted with phenylhydrazine to give the title compound **3a**.

As a comparison, three reactions using ethanol or chlorobenzene [9] as solvent were run to confirm the efficiency of the novel method (Table 1, entries 1–3). It should be mentioned that when ester **1a** was refluxed for 6 h in ethanol in step 1 in the presence of TsOH (10 mol%), no transformation of ester **1a** into ketone **2a** was observed, even though the transformation is achieved in chlorobenzene. To our surprise, hydrazone **3a** was obtained with a yield of 80% when ketone **2a** reacted with phenylhydrazine in ethanol under the refluxing temperature for 4 h in step 2. The results show that the transformation of ester **1a** into ketone **2a** which is a key reagent in the whole reaction needs a high temperature.

**Table 1**  
Effect of catalyst loading on the synthesis of compound **3a**.

Entry	Catalyst (mol%)	Time (min)	Conversion (%) <sup>e</sup>	Yield (%) <sup>f</sup>	
				Step 1	Step 2
1 <sup>a</sup>	1	240	86	60	43
2 <sup>b</sup>	10	360	0	–	–
3 <sup>c</sup>	10	–	–	240	80
4 <sup>d</sup>	–	8	81	6	Trace
5 <sup>d</sup>	1	6	83	6	75
6 <sup>d</sup>	10	4	86	6	78
7 <sup>d</sup>	20	4	88	6	81
8 <sup>d</sup>	30	4	93	6	84
9 <sup>d</sup>	40	4	94	6	82

<sup>a</sup> Reaction conditions: ester **1a** (3.00 mmol), phenylhydrazine (3.60 mmol), TsOH (0.03 mmol), chlorobenzene (30 mL), at the refluxing temperature.

<sup>b</sup> Reaction conditions: ester **1a** (3.00 mmol), TsOH (0.3 mmol), ethanol (30 mL), at the refluxing temperature.

<sup>c</sup> Reaction conditions: ketone **2a** (3.00 mmol), phenylhydrazine (3.60 mmol), TsOH (0.3 mmol), ethanol (30 mL), at the refluxing temperature.

<sup>d</sup> Reaction conditions: ester **1a** (1.00 mmol), phenylhydrazine (1.20 mmol), at 252 W of microwave irradiation.

<sup>e</sup> Determined via HPLC analysis of the crude reaction mixture.

<sup>f</sup> Isolated yields.

To determine the role of the catalyst under the microwave conditions, an experiment in the absence of the catalyst was designed (Table 1, entry 4). Surprisingly, ester **1a** was successfully transformed into ketone **2a** with a conversion of 81% at 252 W of microwave irradiation (MWI) for 8 min even without adding the catalyst in step 1. However, when phenylhydrazine directly reacted with the ketone **2a**, not being isolated from the mixture, in the absence of the catalyst at 252 W of microwave irradiation (MWI) for 6 min in step 2, only trace target compound **3a** was obtained. HPLC analysis shows that many byproducts appeared in the reaction mixture. Obviously, the catalyst TsOH is essential for the formation of the hydrazone **3a** in step 2.

To show the advantages of novel method, our results and reaction conditions for one-pot synthesis of coumarin hydrazone **3a** were compared with the data of the literature method [12] (Table 1). Coumarin hydrazone **3a** was formed with a yield of 75% at 252 W of microwave irradiation for 6 min in step 1 and 6 min in step 2 in the presence of 1 mol% TsOH/SiO<sub>2</sub> (Table 1, entry 5). However, the yield of coumarin hydrazone **3a** was only 43% when ester **1a** was refluxed for 4 h in chlorobenzene in step 1 in the presence of TsOH (1 mol%) to transform into the ketone **2a** and then the isolated ketone **2a** reacted with phenylhydrazine under the refluxing temperature for 1 h using chlorobenzene as solvent and TsOH (1 mol%) as catalyst in the step 2 (Table 1, entry 1) [9]. The main reason of the lower yield in the above literature method was the loss of the ketone **2a** during the process of isolation. Moreover, the isolation process of ketone **2a** was very time-consuming and inconvenient. The results show that the advantages of our synthetic method of coumarin hydrazone over the reported method include a shorter time of implementation, the nonuse of the poisonous solvent and the simple procedure for the unnecessary isolation of the intermediate ketone **2a**.

To optimize the reaction conditions, the effect of catalyst loading on the one-pot reaction for the synthesis of the hydrazone **3a** was investigated by varying catalyst loading from 1 mol% to 40 mol% (Table 1, entries 5–9). The results show that the yield of hydrazone **3a** increased from 75% to 84% for 1–30 mol% of catalyst

**Table 2**  
Effect of microwave power on the synthesis of compound **3a**.

Entry	MW (W)	Time (min)	Conversion (%) <sup>a</sup>	Yield (%) <sup>b</sup>	
				Step 1	Step 2
1	126	10	82	15	80
2	252	4	93	6	84
3	406	2	97	5	81

Reaction conditions: ester **1a** (1.00 mmol), phenylhydrazine (1.20 mmol), TsOH/SiO<sub>2</sub> (30 mol %).

<sup>a</sup> Determined via HPLC analysis of the crude reaction mixture.

<sup>b</sup> Isolated yields.

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