General Microwave-assisted Protocols for the Expedient Synthesis of Furo[3,2-*c*]chromen-4-ones

Jie Wu#
VivoQuest, Inc., 711 Executive Blvd., Suite Q, Valley Cottage, NY 10989, U. S. A.

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Functionalized furo[3,2-*c*]chromen-4-ones are expediently prepared in excellent yields (92–99%) from common 4-hydroxycoumarins, isocyanides, and aldehydes under microwave irradiation.

High-throughput screening has created a critical demand to develop practical routes for rapid chemical synthesis of natural product-like molecules. To secure such practice, the discovery and invention of new synthetic methods and technologies for accessing some natural products entities in more efficient ways have been a fertile area of organic synthesis.[1] Although a variety of synthetic methods exists in the literature, which allows the chemists to synthesize the intriguing molecules individually, however, it is highly desired to develop even more effective synthetic pathways for heterocycle formation in order to build up complex natural product-like molecules in a combinatorial format.

Multicomponent reactions (MCRs) are a powerful tool in the modern drug discovery process in terms of lead finding and lead optimization,[2–7] but the range of easily accessible and functionalized small heterocycles is rather limited. The development of new, rapid, and robust routes toward focused libraries of such heterocycles is therefore of great importance. On the other hand, microwave-assisted organic synthesis (MAOS), fuelled by the development and availability of precision controlled, single-mode microwave reactors, has had a profound impact on the way that chemists approach organic and parallel synthesis. Clearly, reduction in reaction times, improved yields and suppression of side products, relative to traditional thermal heating, are benefits of this emerging technology.[8] Recently, the literature has seen a plethora of MAOS protocols for various chemical transformations; however, the application of MAOS as a diversity engine for parallel synthesis has only begun to accrue.

The prominence of coumarins in natural products and biologically active molecules has promoted considerable efforts toward their synthesis.[9] As a "prevailed" scaffold, furocoumarin (Figure 1) shows interesting biological properties, presumably related to the natural defense of plants against fungal attack.[9] It is inherently photosensitive and found to have therapeutic uses. The photochemotherapeutic effect relies on their ability to intercalate with the pyrimidine bases of microorganism DNA.[10] Our continued interest to build-up a coumarin based combinatorial library led us to devote our efforts to develop efficient pathway for the synthesis of diversified furocoumarin molecules.

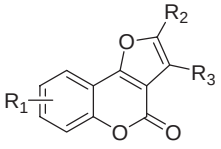
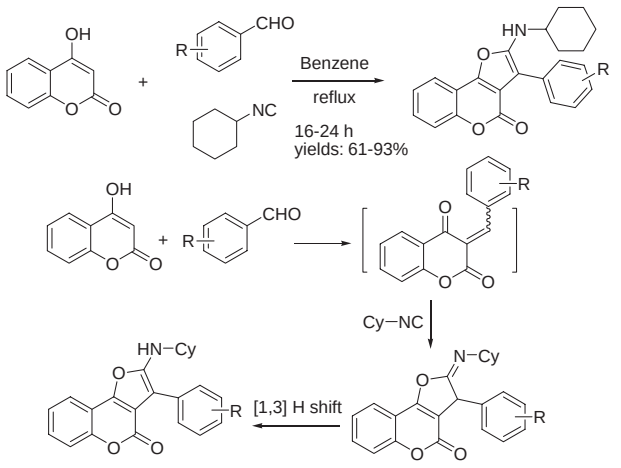


Figure 1. Furocoumarin scaffold.

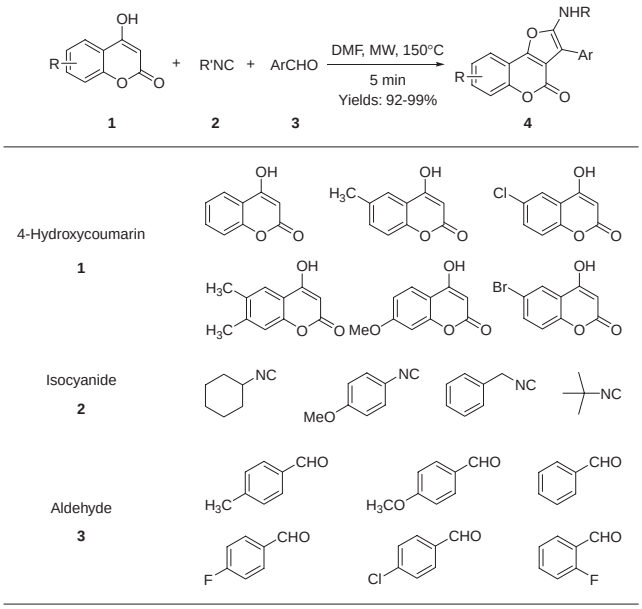
Recently, Nair[11] reported a novel procedure for the synthesis of furocoumarin via the MCRs of 4-hydroxycoumarin with aryl aldehydes and cyclohexyl isocyanide. (Scheme 1) This reaction presumably occurs via a [4 + 1] cycloaddition followed by a [1,3]H shift. However, only several examples were presented in the paper for scope investigation. And in most of the cases, the yields of the desired furocoumarins were moderate. Moreover, extended reaction times of up to 24 h under reflux condition (benzene, >100 °C) were required. These drawbacks restrictedly limit the applications for furocoumarin library construction. Due to the advantages of microwave irradiation in organic synthesis, the use of microwaves, to accelerate reactions, will offer an attractive means of extending the utility of this reaction for use in high throughput library synthesis.

As part of an ongoing program for the construction of natural product-like compounds,[12] we decided to investigate the possibility of using microwaves to accelerate the synthesis of a range of furo[3,2-*c*]chromen-4-ones via a three-component reaction. Initial study was performed by treatment of 4-hydroxycoumarin, 4-chlorobenzaldehyde, and cyclohexyl isocyanide in benzene at 100 °C under microwave irradiation (automated microwave synthesizer, Initiator Eight™, Biotage) in a sealed 5 mL vial (300 W and 10 min). Gratifyingly, we observed the formation of the desired product although the yield was not as good as expected (68%). Further studies established showed that DMF was the best choice of solvent among the solvents (EtOH, benzene, toluene, DMF, and water) screened and the yield was increased to 87%. Next, we surveyed the temperature for the reaction. The result was dramatically improved when the reaction was performed at 150 °C and the reaction time was shortened



Scheme 1.

Table 1. Microwave-assisted three-component synthesis of small size of furocoumarin library[13]



to 5 min (94% yield). This optimized reaction condition was then applied to a number of reactions where the 4-hydroxycoumarin, aldehyde, and isocyanide were varied (Table 1). It is noteworthy that, in general, to make the procedure efficient for library synthesis, all reagents and solvents were used as purchased and no special precautions such as predrying vials or performing the reaction under an inert atmosphere were used.

Six of 4-hydroxycoumarins, four of isocyanides, and six of aldehydes were selected for this small library construction. The substrates were mixed in a combinatorial format and totally 144 reactions were performed. As shown in Table 1, this method is equally effective for both 4-hydroxycoumarins and aldehydes. Various substituted 4-hydroxycoumarins **1**, isocyanides **2**, and aromatic aldehydes **3** reacted smoothly to produce a range of furo[3,2-*c*]chromen-4-ones. Complete conversion and excellent isolated yields were observed for all substrates employed. This reaction is very clean and free from side reactions. The operation is simple, which followed the general procedure[13] and purified via preparative TLC, and totally 144 reactions afforded the desired products in almost quantitative yields (92–99%). For example, treatment of 4-hydroxycoumarin, 4-chlorobenzaldehyde, and cyclohexyl isocyanide under microwave irradiation (300 W, 150 °C, and 5 min) afforded the desired product in 96% yield, while 61% yield (24 h, PhH, and reflux) was generated as reported by Nair.[11] And also, for different type of substrates, the reaction was found to be tolerated a range of different groups with different electronic demands on aromatic rings involving electron-donating and electron-withdrawing groups. The final products of this small library were characterized by ^{1}H and ^{13}C NMR and LC-MS.

In summary, we have developed an efficient and rapid microwave assisted route for the synthesis of a range of furo-[3,2-*c*]chromen-4-ones, which will be applied in different biological assays. Reduction in reaction times, improved yields and suppression of side products make this reaction attractive. The advantages of this method also include good substrate generality and experimental ease. Further construction of other natural product-like compounds via microwave-assisted organic synthesis is under investigation.

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References and Notes

Present address: Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, P. R. China.

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13 General procedure: 4-hydroxycoumarin (0.25 mmol), aldehyde (0.25 mmol), and isocyanide (0.25 mmol) in DMF (3.0 mL) were reacted under microwave irradiation in a sealed vial (300 W and 150 °C) for 5 min (automated microwave synthesizer, Initiator Eight™, Biotage). After washed with water (10 mL) and extracted with ethyl acetate (10 mL), the solvent was evaporated. The resulting residue was purified via preparative TLC to afford the desired product.

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