

# Microwave-assisted, water-mediated Michael addition for synthesis of kojic acid derivatives

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**Abstract** A highly efficient method is described for the synthesis of substituted kojic acid derivatives in the presence of water under microwave irradiation. This transformation represents an efficient way to synthesize kojic acid derivatives from simple starting materials.

**Keywords** Kojic acid · Nitro styrenes · Amino substituted kojic acid derivatives · Microwave conditions

Kojic acid and its analogues have emerged as potential biologically active molecules because of their broad spectrum of activity against various pathogens [1]. It has been known as an additive to prevent browning of food materials in the food industry, as an antioxidant in order to preserve their freshness and to inhibit discoloration [2]. Also, it forms stable complexes of metal kojates via reaction of kojic acid with metal acetate salts [3–5]. Additionally, kojic acid and its derivatives have been shown to possess various bioactivities such as antimicrobial, cosmetic skin-whitening [6], herbicidal [7], anti-speck [8], pesticide [9], antitumor [10], anti-diabetic [11] and antiproliferative activities [12].

In view of the importance of these heterocycles, various synthetic methods have been developed for synthesis of kojic acid derivatives. Reddy et al. [13–15] synthesized kojic acid derivatives from kojic acid, aldehydes and 1,3 diketones or indoles in a neat reaction. Li et al. [16] synthesized amide-substituted kojic acid

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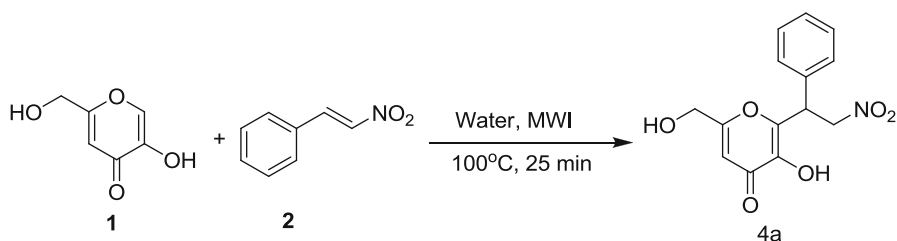
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derivatives from Meldrum's acid, kojic acid and ammonium acetate in ionic liquids as a green (ecologically friendly) protocol. Though the reported methods are satisfactory, they suffer from certain drawbacks, like the use of expensive catalysts, toxic metals, extended reaction times, and environmentally hazardous organic solvents. Synthesis of compounds via a green, mild and simpler procedure, eliminating the use and generation of hazardous substances is the foremost goal of green chemistry today. In particular, microwave irradiation has become a complementary tool in the development of green chemistry. Microwave irradiation with water as a reaction medium is a highly reliable and sustainable chemical approach. Water is a clean and safe solvent which is cheap, non-toxic, non-combustible, non-explosive, and the most benign environmentally. However, water has been rarely used as a solvent for organic reactions due to the poor solubility of most of the organic compounds in water. But at elevated temperatures under microwave irradiation, the physical and chemical properties of water are altered in such a way that it behaves both as a pseudoorganic solvent and a phase transfer catalyst too.

In this communication, we have reported the synthesis of kojic acid derivatives by microwave-assisted, water-mediated reaction (Scheme 1). Initially, we facilitated reaction of kojic acid (**1**) with (E)-(2-nitrovinyl)benzene (**2a**) in the presence of water under microwave irradiation, proceeding smoothly to give the Michael addition product in excellent yield (**4a**).

To check the effectiveness of water as a solvent under similar conditions, a study was made by changing the solvent system of the reaction. As seen in Table 1, a



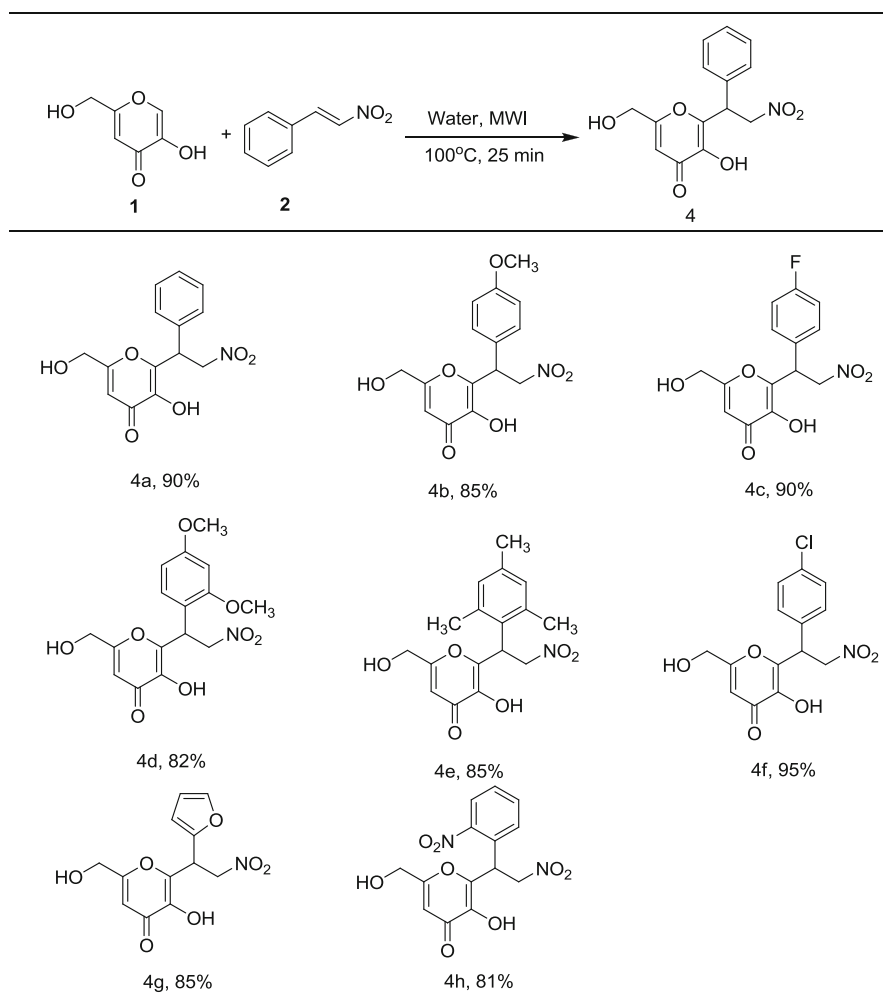
**Scheme 1** Synthesis of kojic acid derivative (**1**) and (E)-(2-nitrovinyl)benzene

**Table 1** Screening of solvents and temperature

Entry	Solvent	Temp (°C)	Yield (%) <sup>a</sup>
1	DMF	110	–
2	DMSO	110	–
3	PEG-400	110	30
4	Ionic liquid	110	55
5	CH <sub>3</sub> CN	90	–
6	Toulene	100	–
7	Water	80	60
8	Water	100	90

Kojic acid (1 mmol) and (E)-(2-nitrovinyl)benzene (1 mmol) in 2 ml of the solvent for 25 min under microwave irradiation

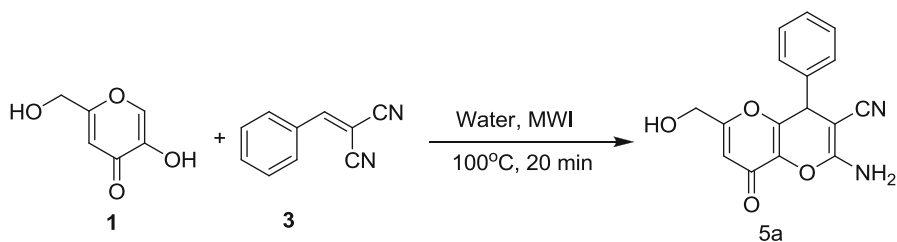
<sup>a</sup> Isolated yield

**Table 2** Synthesis of different nitro-substituted kojic acid derivatives<sup>a</sup>

Isolated yields are given for each derivative in percentage

<sup>a</sup> Reaction conditions: kojic acid 1 (1 mmol), nitro styrene 2 (1 mmol), water 3 ml, 100 °C, MWI

diversity of reaction conditions were employed to discover the optimal reaction conditions, the results of which show that solvents such as toluene and acetonitrile are not right for this reaction, as there is no formation of the desired product even in a trace quantity (Table 1, entries 5–6). When dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were employed as reaction media, the desired product was attained in lower yields (Table 1, entries 1 and 2). However, moving on to check some different greener media, such as polyethylene glycol 400 (PEG-400 and an ionic liquid, the solvents formed the product in moderate yields (Table 1, entries 3 and 4). In addition, among the broad range of solvent systems examined, the



**Scheme 2** Synthesis of amino-fused kojic acid derivatives via Michael addition followed by cyclization

water-mediated reactions were the most successful in terms of yields. Furthermore, shifting the temperature below the optimal 100 °C led to a decrease in yields (Table 1, entry 7). The time duration of the reaction was important mainly because a longer reaction time will result in the formation of by-products.

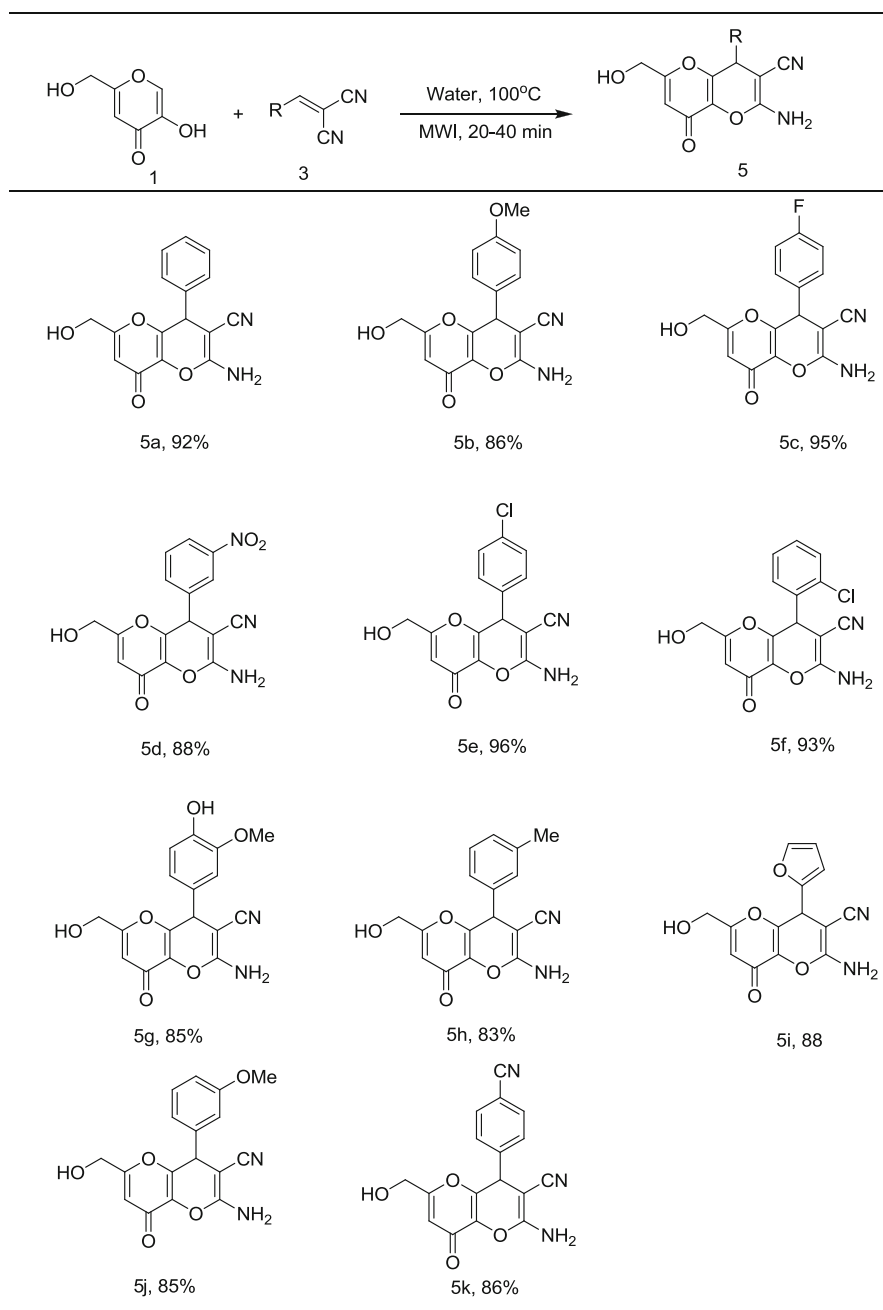
After optimization of experimental conditions, we next extended this process for other (E)-(2-nitrovinyl)benzenes. The scope of the reaction is illustrated with respect to various nitro styrenes and the results are summarized in Table 2. In all cases, we observed good yields. Interestingly, the halogen substituents present on the aromatic ring had shown some effect on the conversion. It was observed that halogen substitute styrene gave the products in high yields than other aromatic counterparts (entries c and f, Table 2). The reaction also works well with hetero aromatic styrene. Respectively, the kojic acid react with hetero aromatic styrene in similar conditions give the desired product in 86 % yield (entry g, Table 2).

Inspired by the results obtained with  $\beta$ -nitro styrenes (2), we turned our attention to extend this process to 2-benzylidenemalononitriles. Accordingly, treatment of kojic acid with 2-benzylidenemalononitrile in the similar conditions afforded the respective amino-substituted, fused kojic acid derivative **5a** as a sole product in 92 % yield (Scheme 2).

Inspired the above results, the scope of the reaction is illustrated with respect to various 2-benzylidenemalononitriles and the results are summarized in Table 3. A variety of substituted 2-benzylidenemalononitriles reacted efficiently with kojic acid to furnish the desired products in good to high yields (85–95 %). Thus, it provides a direct approach for the conversion of kojic acid into fused amino kojic acid derivatives.

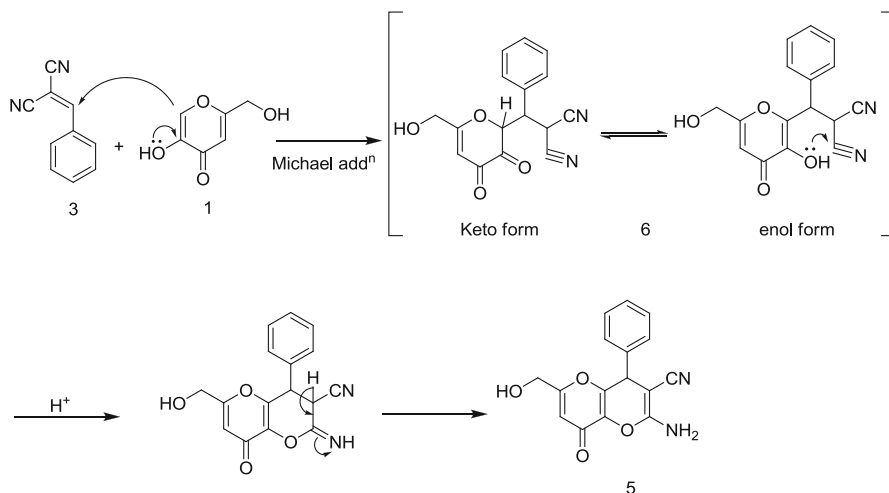
Based on the experimental results, we proposed a plausible mechanism of the microwave-irradiated condensation for the formation of derivative 5, as shown in Scheme 3 [13–15, 17, 18]. Initially, Michael addition of 3 with kojic acid 1 would furnish intermediate 6, which underwent cyclization, aromatization, to give the product 5.

In conclusion, an extremely efficient and green method has been developed for the synthesis of biologically active kojic acid derivatives, by means of microwave irradiation in aqueous medium. The operational simplicity, mild reaction conditions, short reaction time, higher yields, (75–95 %) and environmental friendliness are notable features of this procedure. The method is extensively applicable for the rapid preparation of a library of biologically active kojic acid derivatives.

**Table 3** Synthesis of different nitro-substituted kojic acid derivatives<sup>a</sup>

Isolated yields are given for each derivative in percentage

<sup>a</sup> Reaction conditions: kojic acid 1 (1 mmol), cyano styrenes 3 (1 mmol), water, 100 °C, MWI



**Scheme 3** A plausible reaction mechanism for the formation of 5

## Typical procedure for the synthesis of kojic acid derivatives

A sealed 10-mL glass tube containing kojic acid (1 mmol), 2-benzylidenemalononitriles or nitro styrenes (1 mmol) and water (2 mL) was placed in the cavity of a microwave reactor and irradiated for the appropriate time at 105 °C (temperature monitored by a built-in infrared sensor), and power 160 W. After cooling to room temperature by air flow, the tube was removed from the rotor. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were then dried over anhydrous  $Na_2SO_4$  and after removal of the solvent, the mixture was purified by (silica gel) column chromatography (EtoAc/Hexane, 90:10 as eluent) to give pure products.

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