

Nano silica sulfuric acid catalyzed synthesis of 2-substituted aryl (indolyl) kojic acid derivatives

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ABSTRACT

Nano silica sulfuric acid as a solid acid, was described to be an effective catalyst for one-pot three-component reaction of kojic acid, aryl aldehydes and indoles for the preparation of 2-substituted aryl (indolyl) kojic acid derivatives. High yields, simple operation, easy-work procedure, mild reaction conditions are some advantages of this protocol. The present method does not involve any hazardous organic solvent. Therefore, this procedure could be classified as green chemistry.

Keywords: Kojic acid; Indole; Nano silica sulfuric acid; Aldehyde; Multi-component.

1. Introduction

Recently, multi-component, one-pot syntheses have become one of the most attractive reactions due to their vast applications. These reactions are widely applied in pharmaceutical chemistry for producing different structures and combinatorial libraries for drug discovery [1]. The 3-substituted indole moieties are included in numerous natural products and they are dominant molecules in medicinal chemistry [2,3]. A number of 3-substituted indole derivatives possess wide range of biological activities and pharmacological properties, such as anticancer, anti-tumour [4], anti-inflammatory, hypoglycemic, analgesic and anti-pyretic activities [5]. Many different kinds of indole alkaloids are known as one of the increasing agents in marine invertebrate metabolites for their wide range of biological properties [6,7].

On the other hand, kojic acid is also known as an attractive molecule in pharmaceutical chemistry due to its accessibility, potential biological activity and high reactivity [8,9].

Therefore, a large number of kojic acid derivatives have been prepared for biological assay [10,11].

Due to the vast medicinal utility of kojic acid and 3-substituted indole derivatives, the introduction of a mild, efficient and selective method to synthesize these compounds is still needed. There are only two reports in the literature dealing with the synthesis of 2-substituted aryl (indolyl) kojic acid derivatives [12,13].

Consequently, it is desirable to develop an easy manipulative procedure, as well as to avoid using strong acids or bases, toxic metals and other corrosive media and replacing hazardous or expensive reactants and reagents by safer and economical ones. The use of environmentally friendly solid catalysts can reduce the amount of toxic waste and also facilitate the reactions to occur under milder conditions.

Recently, we reported the preparation of nano silica sulfuric acid as a stable acidic reagent [14] and showed its catalytic activity in synthetic methodology [15].

Here we wish to report the ability of this reagent as an efficient catalyst for the one-pot synthesis of 2-substituted aryl (indolyl) kojic acid derivatives from kojic acid, aryl aldehydes and indole derivatives in high yields (Scheme 1).

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Scheme 1. Preparation of 2-substituted aryl (indolyl) kojic acid derivatives by the reaction of kojic acid with aryl aldehyde and indole derivatives using nano silica sulfuric acid.

2. Experimental

2.1. General

Melting points were determined with an Electrothermal 9100 apparatus. The NMR spectra were recorded in (D₆) DMSO and CDCl₃ on Bruker Avance III 400 MHz spectrometer (400.1 MHz for ¹H and 100.6 MHz for ¹³C). SEM images were obtained using model VEGA/TESCAN with an accelerating voltage of 15 kV. TEM images were obtained using a Philips CM10 microscope operated at 200 kV. Materials were purchased from Fluka and Merck companies.

2.2. Synthesis of nano silica sulfuric acid

The catalyst was prepared by combination of chlorosulfonic acid (23.3 g) drop by drop over 10 min via a syringe to nano silica gel powder (60 g) in a 100 mL flask at 0 °C (ice bath). The reaction mixture was then stirred, and after 30 min, the white powder was formed. The mixture was filtered and resulting powder dried at room temperature [14b]. The catalyst was characterized by SEM and TEM images.

2.3. General procedure for the synthesis of 2-substituted aryl (indolyl) kojic acid derivatives (4)

To a solution of aryl aldehyde **2** (1 mmol), kojic acid **1** (1 mmol), in EtOH (7 mL), was added nano silica sulfuric acid (0.003 g). Then the mixture was stirred at reflux conditions. After 5-15 min indole **3** (1 mmol) was added and the reaction was continued for appropriate time. After the completion of the reaction (as monitored by TLC), the mixture was filtered to remove the catalyst. Then water was added to reaction mixture (15 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum. Finally, the crude product was chromatographed in silica gel (70:30 *n*-hexane/ethyl acetate). All the products were characterized by comparing of melting point and ¹HNMR and ¹³CNMR spectra with those of authentic samples reported in the literatures [12,13].

Selected spectral data

2-((1H-Indol-3-yl)(4-bromophenyl)methyl)-3-hydroxy-6-(hydroxymethyl)-4H-pyran-4-one (4d):

¹HNMR (400 MHz, DMSO-*d*₆ + CDCl₃, 1:4): δ= 4.23-4.27 (m, 2H), 5.57 (s, 1H), 6.19 (s, 1H), 6.67 (s, 1H), 7.03 (t, *J* = 8 Hz, 1H), 7.18-7.26 (m, 2H), 7.37-7.43

(m, 3H), 7.54-7.58 (m, 2H), 7.98 (s, 1H), 10.14 (s, 1H) ppm. ¹³CNMR (100 MHz, CDCl₃): δ= 39.6, 59.2, 111.1, 119.1, 119.4, 119.8, 122.1, 123.6, 126.8, 130.5, 131.3, 133.7, 135.2, 136.7, 138.8, 143.1, 150.2, 167.1, 173.4 ppm.

2-((1H-Indol-3-yl)(2-nitrophenyl)methyl)-3-hydroxy-6-(hydroxymethyl)-4H-pyran-4-one (4e):

¹HNMR (400 MHz, DMSO-*d*₆ + CDCl₃, 1:4): δ= 4.20-4.28 (m, 2H), 5.50 (s, 1H), 6.09 (s, 1H), 6.61 (s, 1H), 7.02-7.21 (m, 3H), 7.37-7.43 (m, 3H), 7.54-7.56 (m, 1H), 7.71-7.74 (m, 1H), 8.09 (d, *J*=8.2, 1H), 10.41 (s, 1H) ppm. ¹³CNMR (100 MHz, CDCl₃): δ= 38.7, 60.1, 111.1, 119.5, 119.7 (2C), 122.2, 123.8 (2C), 124.0, 124.4, 127.2, 128.8, 130.9, 132.3, 135.2, 138.8, 141.4, 150.4, 167.8, 176.3 ppm.

2-((1H-Indol-3-yl)(4-chloro-2-nitrophenyl)methyl)-3-hydroxy-6-(hydroxymethyl)-4H-pyran-4-one (4h):

¹HNMR (400 MHz, DMSO-*d*₆ + CDCl₃, 1:4): δ= 4.23-4.27 (m, 2H), 5.75 (s, 1H), 6.01 (s, 1H), 6.67 (s, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.36-7.55 (m, 4H), 7.86 (s, 1H), 8.05 (s, 1H), 10.23 (s, 1H) ppm. ¹³CNMR (100 MHz, CDCl₃): δ= 39.6, 60.2, 111.2, 119.5 (2C), 120.3, 122.2, 122.9, 123.9 (2C), 127.5, 130.9, 131.4, 132.2, 134.9, 136.5, 137.4, 145.6, 150.5, 167.6, 176.1 ppm.

3. Results and Discussion

On our ongoing program to study the application of solid acid catalysts for the synthesis of 2-substituted aryl (indolyl) kojic acid derivatives [13], we investigated the preparation of these compounds in the presence of various solid acid catalysts such as nano silica sulfuric acid.

Initially, nano silica sulfuric acid was prepared by the method described in literature [14b]. The dimensions of nanoparticles were observed with SEM and TEM images (Fig. 1 and 2). The results confirm the formation of the nano particles, with spherical morphology.

To find optimum reaction conditions, the reaction between benzaldehyde with indole and kojic acid was chosen as model reaction. A series of different catalysts were examined in ethanol (Table 1). Of these catalysts, nano silica sulfuric acid appears to give the best result (Table 1, entry 8).

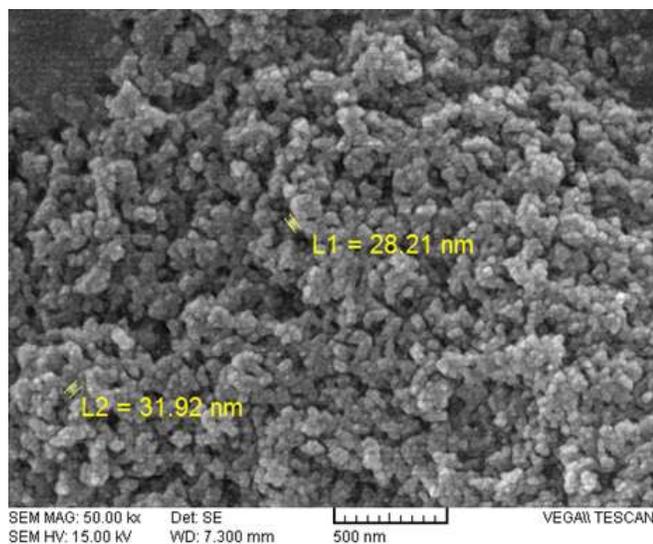


Fig. 1. The SEM image nano silica sulfuric acid.

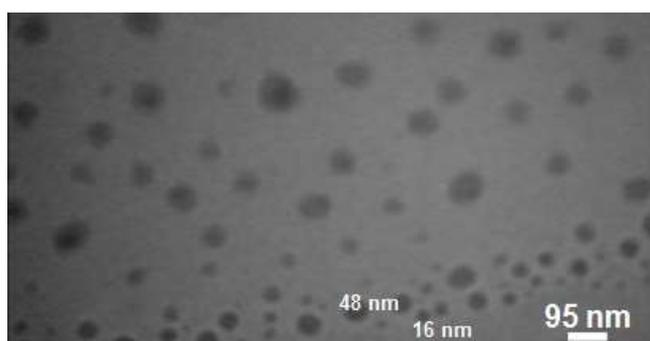


Fig. 2. The TEM image nano silica sulfuric acid.

At the same time a decline in yield was observed by using silica sulfuric acid as catalyst (Table 1, entry 9).

Model reaction carried out in various solvents such as EtOH, THF, H₂O, *n*-hexane, toluene and under solvent free condition, in the presence of nano silica sulfuric acid (Table 2). The results in Table 2, show the efficiency of EtOH which gives the desired product in excellent yield (Table 2, entry 1).

Decreasing the catalyst loading from 0.003 to 0.001 g, lowered the yield of the reaction significantly (Table 3, entries 2-4). The best catalyst loading was found in 0.003 g, which gave an excellent yield of **4a** after only 60 min (Table 3, entry 4). It is worthwhile to mention that reaction temperature was optimized to be reflux in ethanol.

A number of aromatic aldehydes **2** were treated with kojic acid **1** and indole derivatives **3** in the presence of nano silica sulfuric acid (0.003 g) in refluxing EtOH (Table 4).

Benzaldehyde and 2-naphthaldehyde were treated with kojic acid and indole, and the corresponding 2-substituted aryl (indolyl) kojic acid derivatives were produced in excellent yields (Table 4, entries 1 and 9).

Table 1. Effect of different catalysts on the yield of **4a**.^a

Entry	Catalyst	Yield (%)
1	FAU zeolite NPs	60
2	KAl(SO ₄) ₂ .12H ₂ O	50
3	CuCl ₂ .2H ₂ O	35
4	SbCl ₅ -SiO ₂	35
5	SnCl ₂ .2H ₂ O	30
6	ZnSO ₄ . H ₂ O	45
7	Nano ZnO	60
8	Nano SiO ₂ -OSO ₃ H	98
9	SiO ₂ -OSO ₃ H	70
10	Nano SiO ₂ -OSO ₃ H ^{2nd run}	94
11	Nano SiO ₂ -OSO ₃ H ^{3rd run}	92

^aReaction conditions: 60 min at reflux temperature in 10 mL EtOH.

Table 2. Effect of different solvents on the yield of **4a**.

Entry	Solvent	Yield (%)
1	EtOH ^a	98
2	THF ^a	25
3	H ₂ O ^a	50
4	<i>n</i> -Hexane ^a	10
5	Toluene ^a	55
6	Solvent-less ^b	70

^a60 min at reflux temperature in 10 mL solvent.

^b60 min at 110-120°C.

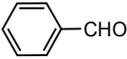
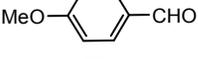
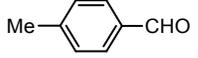
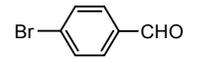
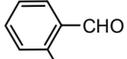
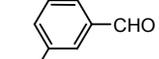
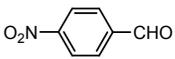
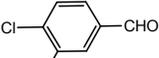
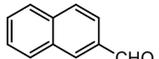
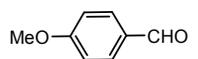
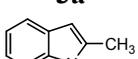
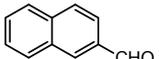
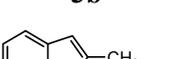
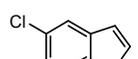
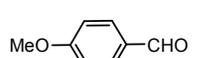
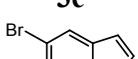
Table 3. Effect of catalyst amount on the yield of **4a**.^a

Entry	Amount of catalyst (g)	Yield (%)
1	-	-
2	0.001	50
3	0.002	70
4	0.003	98

^aReaction conditions: 60 min at reflux temperature in 10 mL EtOH.

Aromatic aldehydes such as 4-methoxy and 4-methyl reacted well with kojic acid and indol to afford desired products in good yields (Table 4, entries 2, 3). When kojic acid and indole reacted with aldehyds including halogen group and electron-withdrawing group on phenyl such as 2-nitro, 3-nitro and 4-nitro benzaldehyde, the corresponding product was formed with 80-85% yields (Table 4, entries 4-8). Interestingly, substituted indoles were also effective for this three-component reaction. When 2-methyl indole reacted with kojic acid and aldehydes such as 4-methoxy

Table 4. Preparation of 2-substituted aryl (indolyl) kojic acid derivatives using nano silica sulfuric acid as a catalyst.

Entry	Aldehyde	Indole	Product ^a	Time (min)	Yield (%) ^b	m.p. (°C)	Ref.
1	 2a	 3a	4a	45	98	78-80	[12]
2	 2b	 3a	4b	50	88	97-98	[12]
3	 2c	 3a	4c	50	92	Oil	[13]
4	 2d	 3a	4d	60	84	86-88	[13]
5	 2e	 3a	4e	75	82	169-170	[13]
6	 2f	 3a	4f	65	83	171-173	[13]
7	 2g	 3a	4g	72	85	168-169	[13]
8	 2h	 3a	4h	75	85	169-170	[13]
9	 2i	 3a	4i	45	93	79-80	[13]
10	 2b	 3b	4j	40	89	89-91	[12]
11	 2i	 3b	4k	45	95	86-87	[12]
12	 2b	 3c	4l	55	89	Oil	[12]
13	 2b	 3d	4m	55	94	Oil	[12]

^aAll the products were characterized by comparing of melting point, ¹H NMR and ¹³C NMR spectra with those of authentic samples reported in the literature.

^bYields refer to isolated products.

Table 5. Comparison of the results of Nano SiO₂-OSO₃H with those of other catalysts reported in the literature in the synthesis of 2-substituted aryl (indolyl) kojic acid derivatives.

Entry	Catalyst	Conditions	Time (min)	Yield (%)	Ref.
1	Nano SiO ₂ -OSO ₃ H	EtOH/ Reflux	40-75	80-98	This work
2	FAU-Zeolite	Solvent free/110°C	45-85	82-97	[13]
3	InCl ₃	Solvent free/120°C	55-85	75-90	[12]

benzaldehyde and 2-naphthaldehyde under the same reaction conditions, a higher yield of the 2-substituted aryl (indolyl) kojic acid obtained in shorter times (Table 4, entries 10, 11).

Similarly when 5-chloro and 5-bromo indole were treated with 4-methoxy benzaldehyde and kojic acid in the presence of nano silica sulfuric acid (0.003 g), a good yield of the corresponding products were obtained (Table 4, entries 12, 13).

An interesting feature of this method is that the reagent can be regenerated at the end of the reaction and can be used several times without losing its activity. To recover the catalyst, after completion of the reaction, the mixture was filtered, and catalyst was washed with EtOH, and then the solid residue dries. This process was repeated for two cycles, and the yield of product **4a** did not change significantly (Table 1, entries 10, 11).

However, in order to show the merits and drawbacks of this catalyst, our results were compared with two catalysts reported in literature. As shown in Table 5, Nano SiO₂-OSO₃H can act as an effective catalyst with respect to reaction times, yields and conditions.

4. Conclusions

In summary, we have developed one-pot synthesis for the preparation of 2-substituted aryl (indolyl) kojic acid derivatives through three-component reactions of kojic acid with indoles and aryl aldehydes in the presence of a catalytic amount of nano silica sulfuric acid in EtOH. By incorporating two biologically potential moieties in a single molecule the biological activity of these compounds may be enhanced. Also we employed nano silica sulfuric acid as an easily available and less costly, less toxic, and operable under environmentally friendly conditions catalyst in this reaction and obtained desired products with high yields. Therefore, this method is green, simple, efficient and convenient for formation of a wide range of 2-substituted aryl (indolyl) kojic acid derivatives.

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