



# Aqua-mediated synthesis of acridinediones with reusable silica-supported sulfuric acid as an efficient catalyst

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## Abstract

A simple approach to the synthesis of acridinediones *via* one-pot three-component condensation of an aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), and ammonium acetate or *p*-toluidine in water with use of silica-supported sulfuric acid as an efficient catalyst is described. Excellent yields, catalyst recovery and reusability, and easy work-up are attractive features of this green protocol. All the synthesized acridinediones were characterized on the basis of their melting-points, elemental analysis and spectral data.

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## 1. Introduction

Multicomponent reactions (MCRs) are a promising, vital field of chemistry because the synthesis of complicated molecules can be achieved rapidly and efficiently without the isolation of intermediates [1]. In MCR condensations, three or more compounds react in a single event, but consecutively, to form a new product, which contains the essential parts of all the starting materials. MCRs meet the requirements of an environmentally friendly process, with fewer synthetic steps and less energy consumption and waste

production. Moreover, MCRs offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions. Therefore, the search for new MCRs and full exploitation of known MCRs is of considerable interest.

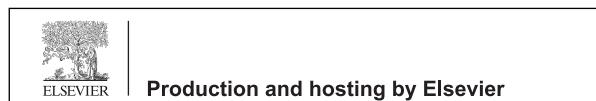
Aqua-mediated reactions have received much attention in organic synthesis because of their environmental safety [2]. Use of clean solvents and heterogeneous, reusable catalysts makes these reactions powerful green chemical technology procedures, resulting in minimal pollution and waste material. Therefore, development of new, water-tolerant, solid, acid catalysts could have major industrial applications [3].

1,4-Dihydropyridines are used commercially as calcium channel blockers in the treatment of cardiovascular diseases, such as hypertension [4]. Recently, dihydropyridines were shown to reverse multidrug resistance in tumour cell lines [5,6]. Acridine-1,8-diones containing a 1,4-dihydropyridine parent nucleus have also attracted considerable attention by their potential pharmacological activity, as acridine and its hydro derivatives are biologically active against malaria [7], cancer [8] and leishmania [9],

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bind to and photo-damage DNA [10], are cytotoxic [11] and block potassium channels [12]. A new scaffold, *N*-(9-(ortho/meta/para-(benzyloxy)phenyl)-3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridin-10(9*H*)-yl) isonicotinamide (H1–3) was found to inhibit hSIRT1 during virtual screening of the in-house database, and a library of compounds was designed, synthesized and tested *in vitro* for hSIRT1 activity [13]. A series of novel imidazolyl derivatives of fully and partially hydrogenated 1,8-acridinediones were synthesized and evaluated for their cytotoxic activity on four human cancer cell lines (HeLa, MCF-7, LS-180, and Raji cells) [14].

Acridinedione dyes are a new class of laser dyes with lasing efficiency comparable to that of coumarin-102 [15,16]. These dyes have been shown to mimic NADH analogues to a greater extent because of their tricyclic structures, which protect the enamine moieties [17]. The design and synthesis of 1,3-dithiol-linked acridinedione functionalized gold nanoparticles was described recently [18], as was the design and synthesis of an acridinedione functionalized gold nanoparticle-based PET anion sensor [19].

1,8-(2*H*,5*H*)-Acridinediones were synthesized with the Hantzsch procedure, which involves thermal reaction of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) with an aldehyde and ammonia. Various methods have been used to synthesize acridinediones, including the microwave [20,21], ionic liquid [22,23], LiBr [24], proline [25], silica-bonded *S*-sulfonic acid [26], ceric ammonium nitrate [27] and methanesulfonic acid [28] catalysts. Acridinediones are also synthesized in aqueous media [29–31]; however, many of the methods described have drawbacks, such as use of hazardous organic solvents, long reaction times, low yields, formation of side products and multistep synthesis. Subsequently, there is a demand and scope for developing an efficient, easy, eco-safe approach to obtain acridinediones.

During our studies on the synthesis of 1,4-dihydropyridine derivatives [32–34], we found that silica-supported sulfuric acid efficiently catalyzed the synthesis of 9-phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H*,5*H*)-acridine-1,8-dione derivatives in the reaction of arylaldehydes, dimedone and ammonium acetate in water at 70 °C. Using a similar protocol, we also synthesized 9-phenyl-3,3,6,6-tetramethyl-10-*p*-tolyl-hexahydroacridine-1,8-dione derivatives from arylaldehydes, dimedone and *p*-toluidine in water at 80 °C. The aim of the study reported here was to synthesize acridinediones with silica-supported sulfuric acid as the catalyst.

## 2. Experimental

### 2.1. Apparatus and analysis

Chemicals were purchased from Merck, Fluka and Aldrich Chemical companies. All yields refer to isolated products unless otherwise stated. <sup>1</sup>H Nuclear magnetic resonance (NMR) (500 MHz) and <sup>13</sup>C NMR (125 MHz) spectra were obtained on a Bruker DRX-500 Avance at ambient temperature, with tetramethylsilane as the internal standard and dimethylsulfoxide (DMSO)-*d*<sub>6</sub> as the solvent. Fourier transform infrared (IR) spectra were obtained as KBr discs on a Shimadzu spectrometer. Mass spectra were determined on a Varian Saturn 2000 gas chromatograph–mass spectrometer. Elemental analyses were conducted with a Perkin Elmer 2400 CHN elemental analyser flowchart.

### 2.2. Preparation of silica sulfuric acid

Silica sulfuric acid was prepared from silica gel and chlorosulfonic acid, as reported by Zolfigol [35]. A 500-mL suction flask was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (23.3 g, 0.2 mol) and a gas inlet tube for conducting HCl gas over H<sub>2</sub>O, the adsorbing solution. Then, 60 g of silica gel were charged into the flask, and chlorosulfonic acid was added dropwise over 30 min at room temperature. HCl gas evolved immediately from the reaction vessel. After the addition was complete, the mixture was shaken for 30 min, and silica sulfuric acid was obtained (76 g) as a white solid. The amount of H<sup>+</sup> in the silica sulfuric acid was determined by acid–base titration: the liberated H<sub>3</sub>O<sup>+</sup> was titrated with standard NaOH, and the amount of H<sup>+</sup> in silica sulfuric acid was calculated (0.05 g equal to 0.13 mmol). This value corresponds to about 95% of the sulfur content, indicating that most of the sulfur species on the sample were in the form of the sulfonic acid groups [36,37].

### 2.3. General procedure for synthesis of 9-phenyl-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(2*H*,5*H*)-acridine-1,8-dione derivatives

A mixture of aldehyde **1** (1 mmol), dimedone **2** (2 mmol), ammonium acetate **3** (1.5 mmol), silica-supported sulfuric acid (0.8 mol%) and water (2 mL) was placed in a 50 mL flask, heated at 70 °C and stirred for the appropriate time as monitored by thin-layer chromatography (hexane:ethyl acetate; 8:2). After completion of the reaction, the mixture was cooled, and the resulting

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