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Article

Cerium (IV) sulfate: A highly efficient reusable heterogeneous catalyst for the one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones under solvent-free conditions

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ABSTRACT

Cerium (IV) sulfate tetrahydrate, $Ce(SO_4)_2·4H_2O$, is a novel inorganic solid acidic catalyst that efficiently catalyzes the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones via the one-pot three-component reaction of isatoic anhydride, aromatic aldehydes, and a nitrogen source (ammonium acetate, ammonium carbonate, ammonium chloride, or methylamine) under solvent-free conditions. The desired products are obtained in short reaction time with high yields. The catalyst is inexpensive and readily available and can be recovered conveniently and reused such that considerable catalytic activity can still be achieved after the fifth run. Easy work-up and avoiding the use of harmful organic solvents are other advantages of this simple procedure.

1. Introduction

Multi-component reactions (MCRs) are a promising and important field of chemistry because the synthesis of complex molecules can be achieved in a fast, efficient, and time-saving manner without the isolation of any intermediates. Organic chemists have therefore become interested in developing novel MCRs or improving known MCRs [1–3]. One such reaction is the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

2,3-Dihydroquinazolin-4(1*H*)-ones are an important class of fused heterocycles with a wide range of pharmacological and biological activities, which include antifertility, antibacterial, antitumor, and antifungal applications [4,5]. Therefore, considerable efforts have been made to explore new simple and direct approaches towards the construction of 2,3-dihydroquinazolin-4(1*H*)-one skeletons. Several methods for the synthesis of these compounds have been reported in the literature. One method involves the condensation of aldehydes with anthranilamide using various promoting agents [6–9], but this is only suitable for the synthesis of 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones. Other methods include reduction of quinazolin-4(3*H*)-ones using sodium borohydride or sodium cyanoborohydride in acetic acid [10], condensation of anthranilamide with benzyl followed by base-catalyzed hydrolysis [11], and a two-step synthesis starting from the reaction of isatoic anhydride and amines, then ring-closing with ketones [12]. The most straightforward procedure for the preparation of 2-substituted- and 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-ones involves the one-pot three-component reaction of isatoic anhydride, aromatic aldehydes, and a nitrogen source such as ammonium acetate or primary amines in the presence of various catalysts. These catalysts include [bmim]HSO_4 [13], silica sulfuric acid [14], *p*-toluenesulfonic acid-paraformaldehyde copolymer (copolymer-PTSA) [15], trifluoroethanol [16], thiamine hydrochloride [17], Cu-CNTs nanocomposite under microwave irradiation [18], aluminum methanesulfonate [19],

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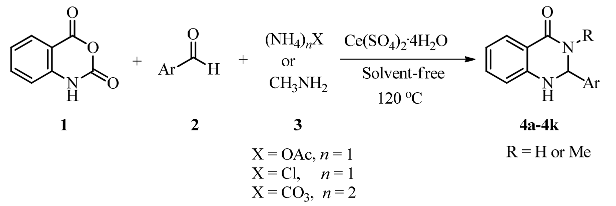
montmorillonite K-10 [20], silica-bonded *S*-sulfonic acid [21], acetic acid [22], $KAl(SO_4)_2·12H_2O$ [23], silica-bonded *N*-propylsulfamic acid [24], and magnetic Fe_3O_4 nanoparticles [25]. However, some of these methods have disadvantages such as long reaction time, expensive catalysts, and using microwave irradiation for accelerated synthesis. Therefore, the discovery of a new and efficient catalyst with high activity, short reaction time, and simple work-up for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones is of prime interest.

Recently cerium (IV) salts have been used for many organic transformations such as the synthesis of carboxylic esters from alkenes [26], synthesis of acetamido phenols [27], conversion of oximes into aldehydes and ketones [28], and one-pot synthesis of 3-acylisoxazoles or polyhydroquinolines [29,30]. The cerium (IV) salts act as Lewis acids in all of these reactions. To the best of our knowledge there are no examples of the use of $Ce(SO_4)_2·4H_2O$ as catalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

As part of our research program directed towards the development of expedient methods using reusable catalysts for the synthesis of organic compounds [31–38], we have recently successfully applied $Ce(SO_4)_2·4H_2O$ to the synthesis of tetrahydrobenzo[*a*]xanthene-11-ones [39] and in the protection of aldehydes as 1,1-diacetates [40] under solvent-free conditions. This reusable heterogeneous solid acidic catalyst performs well and shows high catalytic activity. These results encouraged us to investigate the use of $Ce(SO_4)_2·4H_2O$ in the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in a one-pot three-component reaction of isatoic anhydride **1**, aromatic aldehydes **2**, and a nitrogen source **3** (ammonium acetate, ammonium carbonate, ammonium chloride, or methylamine) under solvent-free conditions.

2. Experimental

A general procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones **4a**–**4k** is as follows. A mixture of isatoic anhydride **1** (1 mmol), an aromatic aldehyde **2** (1 mmol), a nitrogen source (ammonium acetate 1.2 mmol, ammonium carbonate 0.6 mmol, ammonium chloride 1.2 mmol, or methylamine 1.2 mmol), and $Ce(SO_4)_2·4H_2O$ (0.03 mmol, 3 mol% based on isatoic anhydride) was heated in an oil bath at 120 °C for 30–50 min and monitored by TLC. Upon completion of the transformation, the reaction mixture was cooled to room temperature, and hot ethanol was added. The precipitated catalyst was collected by filtration, and the filtrate was cooled to room temperature. The crude product was collected and recrystallized from ethanol to give compounds **4a**–**4k** (Scheme 1).



Scheme 1. $Ce(SO_4)_2·4H_2O$ catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

The melting points were recorded using a Stuart SMP3 melting point apparatus. The IR spectra of the products were obtained with KBr disks using a Tensor 27 Bruker spectrophotometer. The ^1H NMR spectra were recorded using Bruker 400 MHz and 500 MHz spectrometers.

3. Results and discussion

We first examined the reaction by using isatoic anhydride (1 mmol), benzaldehyde (1 mmol), and ammonium acetate (1.2 mmol) as model substrates for the synthesis of compound **4a**. We decided to investigate the efficiency of $Ce(SO_4)_2·4H_2O$ in the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones under solvent-free conditions, which offers several advantages such as being environmentally friendly, simpler work-ups, cleaner products, enhanced selectivity, reduction of by-products, and faster reactions. To find the optimum reaction conditions, different parameters were studied for the formation of compound **4a**. The results are summarized in Table 1. First, the model reaction was carried out without any catalyst at high temperature under solvent-free conditions. No product was observed even after prolonged reaction time (entry 1). Varying the percentage of the catalyst showed that 3 mol% of $Ce(SO_4)_2·4H_2O$ is sufficient to push the reaction to completion within 45 min (entry 7). The effect of reaction temperature on the output was also investigated, and the optimum temperature was found to be 120 °C (entry 7). Next, the reaction was performed in the presence of 3 mol% of $Ce(SO_4)_2·4H_2O$ in different solvents including EtOH, H_2O, CH_2Cl_2, and CH_3CN. As shown, low to moderate yields were obtained in the tested solvents. Therefore, our optimized conditions are 3 mol% of $Ce(SO_4)_2·4H_2O$ at 120 °C under solvent-free conditions. All subsequent reactions were carried out using these conditions.

To determine the scope of the novel protocol, a range of 2,3-dihydroquinazolin-4(1*H*)-ones were prepared by the reaction of isatoic anhydride, aromatic aldehydes, and ammonium

Table 1
Optimization of reaction conditions for the synthesis of compound **4a** catalyzed by $Ce(SO_4)_2·4H_2O$.

Entry	Catalyst (mol%)	Solvent	*T* (°C)	Time (min)	Isolated yield (%)
1	—	—	120	120	—
2	1	—	100	120	59
3	1	—	120	90	72
4	3	—	90	90	58
5	3	—	100	60	71
6	3	—	110	60	83
7	3	—	120	45	95
8	3	—	140	50	94
9	5	—	100	60	72
10	5	—	110	60	82
11	5	—	120	45	93
12	7	—	120	50	92
13	3	EtOH	Reflux	120	58
14	3	H_2O	Reflux	120	41
15	3	CH_2Cl_2	Reflux	120	30
16	3	CH_3CN	Reflux	120	45

Reaction conditions: isatoic anhydride 1 mmol, benzaldehyde 1 mmol, ammonium acetate 1.2 mmol.