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ORIGINAL PAPER

Synthesis of 3-aryl-4(3*H*)-quinazolinones from anthranilic acid, ortho esters, and anilines using $Ce(CH_3SO_3)_3 \cdot 2H_2O$ as catalyst

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Abstract 3-Aryl-4(3*H*)-quinazolinones were synthesized efficiently by the three component one-pot cyclocondensation of anthranilic acid, ortho esters, and anilines in the presence of $Ce(CH_3SO_3)_3 \cdot 2H_2O$ at room temperature under solvent-free conditions. This method offers several advantages, such as a simple procedure, mild reaction conditions, short reaction time, and reusability of the catalyst.

Keywords 3-Aryl-4(3*H*)-quinazolinone · Methanesulfonates · One-pot synthesis · Solvent-free conditions

Introduction

Compounds with biological activity are often derived from heterocyclic structures. 4(3*H*)-Quinazolinones are one such class of bioactive fused heterocycles that are widely used as antimalarial, antitumor, anticonvulsant, antiinflammatory, fungicidal, and antimicrobial agents [1–6]. In addition, 4(3*H*)-quinazolinones are present in several bioactive natural products [7, 8]. Among various types of 4(3*H*)-quinazolinones, 3-substituted 4(3*H*)-quinazolinone derivatives form an important component because they are associated with a wide spectrum of biological activities. Owing to the importance of 3-substituted 4(3*H*)-quinazolinones, different strategies for their synthesis have been described in literature [9, 10]. The most direct approach involves one-pot cyclocondensation of anthranilic acid, ortho esters, and amines in the presence of various catalysts such as $NaHSO_4$ or Amberlyst-15 [11], Yb(III)-resin [12], $Yb(OTf)_3$ [13], $Bi(TFA)_3$-[nbp]$FeCl_4$ [14], $La(NO_3)_3 \cdot 6H_2O$ or *p*-toluenesulfonic acid [15], Keggin-type heteropolyacids under microwave irradiation [16], $SnCl_4 \cdot 4H_2O$ [17], and SiO_2–$FeCl_3$ [18]. However, some of these methods are associated with certain drawbacks such as expensive catalyst, high temperature (60–80 °C), long reaction time (20 h), and using harmful organic solvents. These processes also generate waste-containing solvents and catalysts, which have to be recovered, treated, and disposed of. Therefore, there is still a need to develop green and efficient methods for the synthesis of 3-substituted 4(3*H*)-quinazolinones.

In the past decade, the increasing attention on environmental protection has influenced both academic and industrial groups to develop new chemical processes with maximum yield and minimum cost. The organic reaction should be carried out using non-toxic reagents, catalysts, and solvents or even better, without solvents. Lanthanide methanesulfonates such as water-stable Lewis acid catalysts in organic synthesis have been well documented in recent years [19, 20]. In the course of our investigation to develop new synthetic methods in solvent-free conditions, we found that the one-pot cyclocondensation of anthranilic acid, ortho esters, and anilines can proceed smoothly in the presence of cerous methanesulfonate ($Ce(CH_3SO_3)_3 \cdot 2H_2O$) at room temperature under solvent-free conditions (Scheme 1). After reaction, the catalyst can be recovered and can be recycled at least three times without distinct loss in its catalytic activity.

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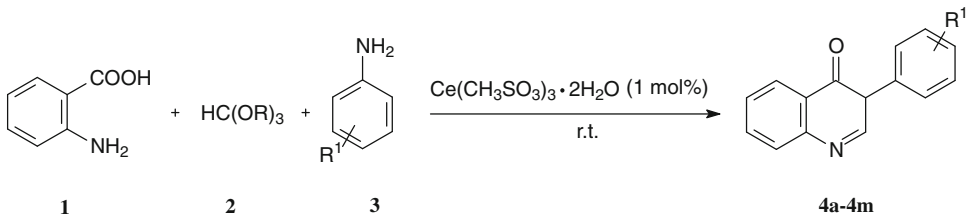
Scheme 1



1 2 3 4a-4m

Results and discussion

First, we compared the catalytic activity of $Ce(CH_3SO_3)_3 \cdot 2H_2O$ with protonic acids, conventional Lewis acids, and other lanthanide methanesulfonates in the model condensation of anthranilic acid with triethyl orthoformate and aniline (Table 1). The results revealed that $Ce(CH_3SO_3)_3 \cdot 2H_2O$ was the most effective catalyst for this transformation since it resulted in the highest conversion to the desired product. Although lanthanide methanesulfonates have similar properties, the catalytic activity of $Ce(CH_3SO_3)_3 \cdot 2H_2O$ in this case is higher than that of other lanthanide methanesulfonates, and $Ce(CH_3SO_3)_3 \cdot 2H_2O$ produced almost quantitative yields of the product. We next sought to probe whether the catalyst could be recycled. After the reaction, CH_2Cl_2 was added to the reaction mixture, and $Ce(CH_3SO_3)_3 \cdot 2H_2O$ could be recovered by simple phase separation and then reused for the next condensation without any treatment. The synthesis of product **4a** under the conditions described in Table 1 with $Ce(CH_3SO_3)_3 \cdot 2H_2O$ as catalyst was run for three consecutive cycles, furnishing the corresponding 3-phenylquinazolin-4(3*H*)-one with 99, 96, and 92% isolated yields (entry 9). The feasibility of the catalyst for recycling may be attributed to the insolubility of rare earth methanesulfonates in the reaction mixture.

To explore the scope and limitations of this reaction, we extended the condensation of anthranilic acid (**1**) with trimethyl or triethyl orthoformate **2** and different substituted anilines **3** in the presence of $Ce(CH_3SO_3)_3 \cdot 2H_2O$, and the results are summarized in Table 2. In all cases, the reactions proceeded very efficiently with anilines carrying electron-donating or electron-withdrawing groups, and steric effects did not influence the yield significantly. However, in previous studies anilines having electron-withdrawing substitutes, e.g., Cl and NO_2, gave generally no products at room temperature due to the decreased electron density of the aromatic system. In this study, the reaction could tolerate different functional groups, such as Me, MeO, Cl, Br, and NO_2, present in the anilines. Moreover, the reaction conditions are mild enough not to produce any undesirable side products. The condensation yield with trimethyl orthoformate was lower than with triethyl orthoformate. Furthermore, trimethyl orthoformate required a comparatively longer reaction time. In addition to aniline derivatives, alkyl amines such as benzyl amine and butylamine were also investigated, and few products were detected. This is probably due to the inductive effect of the aromatic ring that results in the hydrogen atom of aromatic amino groups being released more easily than that of alkyl amines. Therefore, aromatic amines are more active than alkyl amines in this type of reaction.

Table 1 One-pot reaction of anthranilic acid, triethyl orthoformate, and aniline catalyzed by various catalysts

Entry	Catalyst	Time (h)	Isolated yield (%)
1	None	1	5
2	HOAc	1	56
3	$CuCl_2 \cdot 2H_2O$	1	50
4	$AlCl_3 \cdot 6H_2O$	0.5	67
5	$La(CH_3SO_3)_3 \cdot 2H_2O$	1	84
6	$Pr(CH_3SO_3)_3 \cdot 2H_2O$	1	91
7	$Yb(CH_3SO_3)_3 \cdot 2H_2O$	1	92
8	$Nd(CH_3SO_3)_3 \cdot 2H_2O$	1	94
9	$Ce(CH_3SO_3)_3 \cdot 2H_2O$	1	99, 96, 92[a]

Reaction conditions: anthranilic acid (10 mmol), triethyl orthoformate (12 mmol), aniline (12 mmol), catalyst (0.1 mmol), r.t.

[a] Catalyst was reused for three runs

A mechanism for this reaction can be postulated as shown in Scheme 2. The first step in this reaction involves the $Ce(CH_3SO_3)_3 \cdot 2H_2O$ catalyzed formation of imidic ester **5**, which is stabilized by $Ce(CH_3SO_3)_3 \cdot 2H_2O$. The imidic ester **5** may be very prone to react with an aniline **3**, thus leading to the amidine intermediate **6**. Then, the amidine intermediate **6** cyclizes to form the quinazolinone **4** and releases the catalyst for the next run. A similar mechanism had also been described by Wang et al. [13] and Ighilahriz et al. [16].

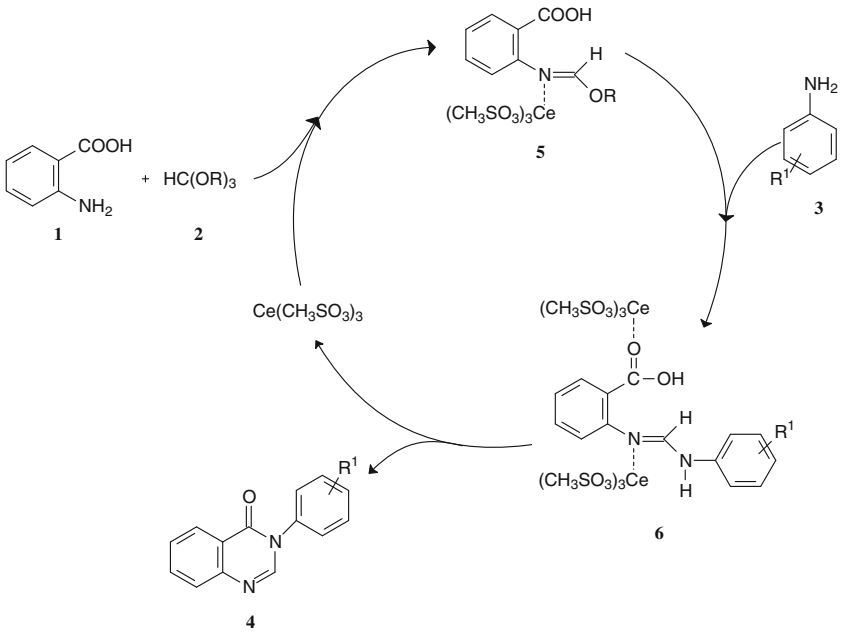
In conclusion, we have demonstrated that 3-aryl-4(3*H*)-quinazolinones can be synthesized easily in short reaction time (0.1–4 h) with excellent yields (42–99%) starting from an anthranilic acid, orthoesters, and anilines in the presence of $Ce(CH_3SO_3)_3 \cdot 2H_2O$ at room temperature. After reaction, the catalyst could be recovered and reused for successive reactions. The method is environmentally benign. We believe our procedure will find important application in the synthesis of 3-aryl-4(3*H*)-quinazolinones and their derivatives.

Table 2 $Ce(CH_3SO_3)_3{\cdot}2H_2O$-catalyzed synthesis of 3-aryl-4(3*H*)-quinazolinones **4a–4m**

Cpd.	R^1	R = Et		R = Me		Mp (°C)	
		Time (h)	Yield (%)	Time (h)	Yield (%)	Found	Reported
4a	H	1	99	2	67	138–140	139–140 [13]
4b	2-Me	1.1	93	1.5	72	158–159	158–189 [21]
4c	3-Me	2	67	3.5	45	137–139	136–137 [13]
4d	4-Me	0.5	95	1	91	145–147	146–147 [13]
4e	2-MeO	0.9	87	4	60	150–152	151–153 [21]
4f	4-MeO	0.4	97	1	92	135–137	132–134 [21]
4g	2-Cl	0.2	78	0.3	62	118–120	117–120 [21]
4h	4-Cl	0.3	82	0.6	62	125–126	122–124 [21]
4i	4-Br	0.2	98	0.4	76	145–147	149–151 [21]
4j	$2\text{-}NO_2$	4	59	0.2	42	149–151	156–158 [13]
4k	$3\text{-}NO_2$	0.2	98	0.1	88	151–153	154–156 [13]
4l	$4\text{-}NO_2$	0.2	98	0.1	83	166–168	165–166 [13]
4m	4-COOH	0.2	84	0.3	57	240–242	240–242 [21]

The structures of the products were determined from spectral and analytical data (IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis) and by comparison with reported data

Scheme 2



Experimental

Melting points were determined using an RY-1 micro-melting point apparatus. Infrared spectra were recorded on a VARIAN Scimitar 2000 series Fourier transform instrument. ^{1}H NMR spectra were recorded on a Bruker AV-500 spectrometer in DMSO-d_6 using TMS as an internal standard. ^{13}C NMR spectra were performed on a Bruker AV-500 spectrometer at 125 MHz using DMSO-d_6 as an internal standard. Elemental analyses were carried out on EA 2400II elemental analyzer (Perkin-Elmer).

General procedure for the synthesis of 3-aryl-4(3H)-quinazolinones ***4***

$Ce(CH_3SO_3)_3{\cdot}2H_2O$ (0.1 mmol) was added to a mixture of anthranilic acid (10 mmol), an orthoester (12 mmol), and an aniline (12 mmol). The mixture was stirred at room temperature (monitored by TLC). After completion, CH_2Cl_2 was added to dissolve the solid product. Then, the catalyst was removed by gravity filtration and dried for its next use. The organic filtrate was evaporated to yield the crude product. The crude product was recrystallized from

ethanol to give the pure products. The pure products were identified by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

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