

Zirconyl(IV) Chloride Catalyzed Three Component One-pot Synthesis of Quinazolin-4(3H)-ones

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Summary. An efficient one-pot method for synthesis of an array of quinazolin-4(3H)-ones from anthranilic acid, triethyl orthoformate, and amines using $ZrOCl_2$ is described. This method offers improvements for the synthesis of quinazolin-4(3H)-ones with regard to short reaction time, yield of products, and simplicity in operation.

Keywords. Quinazolin-4(3H)-ones; $ZrOCl_2$ catalyst; Anthranilic acid; Amines; Triethyl orthoformate.

Introduction

Quinazolines from natural and synthetic origin represent an important heterocyclic class with diverse biological activities [1–6]. At present, some synthetic quinazoline-based drugs, such as metolazone, quine-thazone, and prazosin have achieved medicinal approval for their unique pharmacological indices, and many others are under clinical evaluation [7, 8]. Of the different quinazoline derivatives quinazolin-4(3H)-ones are the most important intermediates in the synthesis of different recent anticancer quinazolines [9]. As a consequence of these important properties, many approaches have been developed to synthesize quinazolin-4(3H)-ones. Usually, 4H-3,1-benzoxazin 4-ones [10] and anthranilic acid [11, 12] have been used as a starting materials.

However, in spite of their potential utility some of the reported methods suffer from drawbacks, like longer reaction time, unsatisfactory yields, cumbersome product isolation, and multi-step synthesis. Thus, there is still need of a simple and general procedure for one-pot synthesis of quinazolin-4(3H)-ones under mild conditions.

In continuation of our ongoing research for the development of simple and efficient methods for the synthesis of various heterocyclic compounds [13], herein we wish to report a simple, economic, and efficient one-pot method for the synthesis of quinazolin-4(3H)-ones using anthranilic acid, substituted anilines, and triethyl orthoformate as substrates in presence of the zirconyl(IV) chloride catalyst.

Zirconyl(IV) chloride is a moisture stable, readily available, and inexpensive oxy-salt of zirconium, which is not much explored in synthetic organic chemistry as a mild and versatile *Lewis* acid catalyst. Compared to conventional *Lewis* acids, zirconyl(IV) chloride has the advantages of low catalyst loading, moisture stability, and catalyst recycling. In the present work, we have demonstrated the ability of $ZrOCl_2$ as a catalyst for the synthesis of an array of substituted quinazolin-4(3H)-ones.

Results and Discussion

Initially, we studied the catalytic property of $ZrOCl_2$ for the synthesis of quinazolin-4(3H)-ones **4** using

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Table 1. Optimization of reaction conditions and the quantity of $ZrOCl_2 \cdot 8 H_2O$ for the synthesis of 3-phenyl-quinazolin-4(3*H*)-one (**4a**)

Solvent	Mol% $ZrOCl_2 \cdot 8H_2O$	Reaction time/min	Yield/ %
<i>THF</i>	20	60	85
Acetonitrile	20	50	91
Ethanol	20	30	98
Ethanol:water (3:1)	20	30	98
Ethanol:water (3:1)	15	30	98
Ethanol:water (3:1)	10	30	98
Ethanol:water (3:1)	05	60	91

anthranilic acid, aniline, and triethyl orthoformate to yield **4a** as an example in various solvents like *THF*, acetonitrile, and ethanol. Among the results obtained, use of 10 mol% $ZrOCl_2$ in ethanol–water gave the best yield (98%) for the synthesis of **4a** (Table 1). The use of environmentally benign solvent, such as water, has got very much importance in ‘Green Chemistry’. To study this aspect, the reaction was carried out for the synthesis of **4a** using 10 mol% $ZrOCl_2$ and the corresponding substrates in water. The reaction was found to be sluggish, and this may be due to the low solubility of the substrates. To avoid this problem, the ethanol:water solvent (3:1; *v/v*) was used and found to be effective

for the synthesis of **4a** (98% in 30 min). The methodology was extended for the synthesis of an array of quinazolin-4(3*H*)-ones using different anilines (Table 2). Good yields were obtained for synthesis of all the quinazolin-4(3*H*)-one derivatives. All synthesized derivatives were characterized using mass and 1H NMR spectroscopy. The present method was found to be effective for both electron-donating and electron-withdrawing substituted anilines.

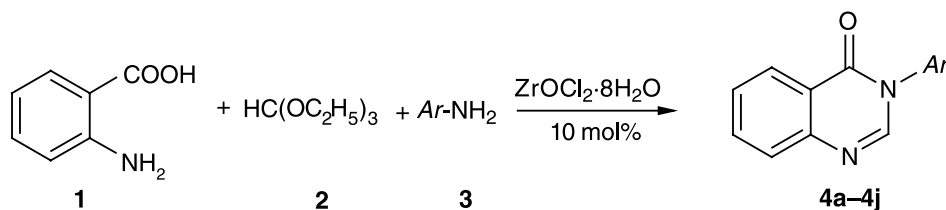
In conclusion, quinazolin-4(3*H*)-ones were efficiently synthesized with high yields using 10 mol% $ZrOCl_2$ as the catalyst. For all the presented reactions, the ethanol–water solvent was used, which is relatively environmentally benign and supporting Green Chemistry. The advantages of the reported method are the use of a cheap catalyst, shorter reaction times, easy work-up, and better yields. Hence the utility of $ZrOCl_2$ catalyst for synthesis of quinazolin-4(3*H*)-ones would be a precious addition to available methods.

Experimental

Melting points were determined in capillary tubes. The 1H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer. Mass spectra were taken with Micromass – QUATTRO-II of WATERS mass spectrometer.

Table 2. $ZrOCl_2$ -catalyzed synthesis of quinazolin-4(3*H*)-ones derivatives

Compound	<i>Ar</i> of $ArNH_2$	Time/min	Yield/%	mp/°C	
				Found	Ref. [12]
4a	<i>Ph</i> –	30	98	139–140	139–140
4b	<i>2-Me-Ph</i> –	40	90	136–137	137–138
4c	<i>3-Me-Ph</i> –	50	90	137–138	136–137
4d	<i>4-Me-Ph</i> –	40	97	145–146	146–147
4e	<i>2-Cl-Ph</i> –	50	90	180–181	180–181
4f	<i>4-Cl-Ph</i> –	30	96	179–180	182–183
4g	<i>3,4-diMe-Ph</i> –	50	98	136–138	134–135
4h	<i>2-NO₂-Ph</i> –	40	90	154–155	156–158
4i	<i>3-NO₂-Ph</i> –	40	92	154–155	154–156
4j	<i>4-NO₂-Ph</i> –	30	98	166–167	165–166

**Scheme 1**

Typical Experimental Procedure for the Synthesis of 3-Phenylquinazolin-4(3H)-ones (4a)

A mixture of 1.37 g anthranilic acid (10 mmol), 1.13 g aniline (1.1 cm³, 12 mmol), 1.9 g triethyl orthoformate (2.1 cm³, 13 mmol), and 0.32 g ZrOCl₂ (1 mmol) in 20 cm³ ethanol: water (3:1; v/v) was heated at 60°C until completion of reaction (monitored by TLC). The reaction mixture was diluted with water and extracted with 3 × 10 cm³ ethyl acetate. The combined organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to afford the crude compound. The crude compounds were purified by recrystallization with ethyl acetate:*n*-hexane (2:8) to afford 2.19 g **4a** (98%) in pure form.

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