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Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by zirconium (IV) chloride as a mild and efficient catalyst

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Abstract

2,3-Dihydroquinazolin-4(1*H*)-ones have been synthesized in the high to excellent yields *via* condensation of 2-aminobenzamide with aldehydes and ketones in the presence of catalytic amount of $ZrCl_4$ in EtOH at room temperature. Mild reaction conditions, clean reaction media, simple workup and easy purification are advantages of this methodology.

Keywords: 2,3-Dihydroquinazolin-4(1*H*)-one; $ZrCl_4$; Catalysis; 2-Aminobenzamide

2,3-Dihydroquinazolin-4(1*H*)-ones are an important class of heterocyclic compounds that have been attracted considerable attention. The natural quinazolinones and their synthetic analogous have been reported to possess a wide range of pharmacological and biological activities including antimalarial [1], antibacterial [2], anticonvulsant [3], anticancer [4] and antifungal [5] activities. Several methods for the synthesis of these compounds have been reported. Among them, the general method includes condensation of aldehydes or ketones with 2-aminobenzamide in the presence of acid catalysts, such as $Sc(OTf)_3$ [6], NH_4Cl [7], *p*-TsOH [8], $CuCl_2$ [9] and $[Bmim]PF_6$ [10]. Three-component reaction of isatoic anhydride, aldehyde and amine [10–14], reduction cyclization of *o*-nitrobenzamides and orthoformate, aldehydes or ketones [15] and reduction of quinazolin-4(3H)-ones [16] are also reported for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. However, most of reported methods suffer from some limitations such as long reaction times, harsh reaction conditions, low yields, tedious workup and multistep reaction. Therefore, mild, simple and efficient processes for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones are still in demands.

$ZrCl_4$ is an air and moisture tolerant, readily available Lewis acid catalyst possessing low toxicity [LD_{50} ($ZrCl_4$, oral rat) = 1.688 mg kg^{-1}] and ease and safety of handling. These salient features along with the strong coordinating ability of Zr^{4+}, makes it a potential catalyst [17,18]. $ZrCl_4$ has already been used as catalyst for various organic transformations [17–19].

In continuation of our previous work for the synthesis of pharmaceutically important heterocycles [20–22], herein, we report the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones *via* the condensation reaction of 2-aminobenzamide with aldehydes and ketones in the presence of catalytic amount of $ZrCl_4$ in EtOH at room temperature (Scheme 1).

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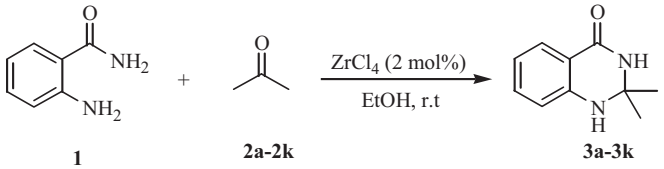


Scheme 1.

Initially, the reaction condition was optimized in the reaction of 2-aminobenzamide and benzaldehyde as model reaction. The results of optimization experiments were summarized in Table 1. Among all the solvents screened, EtOH is the best. The model reaction was carried out in the presence of various amounts of $ZrCl_4$ and in the terms of reaction time and yield of the product, 2 mol% of the catalyst was selected as the best amount of the catalyst. It is noticeable that, the reaction has shown the best time in the presence of 10 mol% $ZrCl_4$, but the yield was low in this condition because of production of byproduct. Water tolerant of the $ZrCl_4$ in the reaction media was investigated by performing the model reaction in the presence of 8 mol% HCl (the same equivalent of 2 mol% $ZrCl_4$). The reaction was completed after 15 min with 83% yield of products. Comparison of this result with result obtained in the presence of 2 mol% $ZrCl_4$ suggest that $ZrCl_4$ has stability toward low amount of water and hydrolysis of $ZrCl_4$ to HCl could not take place in the presence of trace of water. This result can also suggest that the progress of hydrolysis is too slow in the presence of low amount of water that does not have significant effect on the results of reaction. However, low yield of product and presence of byproduct using 10 mol% $ZrCl_4$ (Table 1, entry 1) may be due to hydrolysis of $ZrCl_4$ to trace of HCl due to the presence of higher amount of $ZrCl_4$ in the reaction media.

Following the obtained results, the reaction of 2-aminobenzamide and benzaldehyde was carried out in the presence of 2 mol% $ZrCl_4$ in EtOH at room temperature and the corresponding 2,3-dihydroquinazolin-4(1*H*)-one was obtained in 95% yield (Table 2, entry 1). The scope and generality of this method was investigated in the reaction of various types of aldehydes with 2-aminobenzamide. Aldehydes with both electron-donating and electron-withdrawing substituents were reacted with 2-aminobenzamide at the same reaction conditions and the corresponding 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones were obtained in the 82–97% yields (Table 2, entries 2–8). 2-Furyl-2,3-dihydroquinazolin-4(1*H*)-one was also obtained using 2-furaldehyde as starting material in good yield at short reaction time. Cyclic ketones were also condensed with 2-aminobenzamide successfully and the corresponding 2,3-dihydroquinazolin-4(1*H*)-one with spiro structure were obtained in good yields at short reaction times (Table 2, entries 10 and 11).

It is noteworthy that the reaction procedure is very clean without any undesirable side reaction. The workup and purification procedure was also very simple. After completion of the reaction (monitored by TLC) cold water was added to the reaction mixture and the precipitate was filtered. The crude products were obtained with very high purity. Further purification was achieved by recrystallization from ethanol:water.

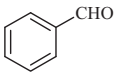
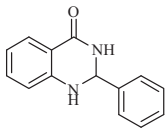
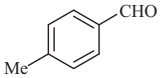
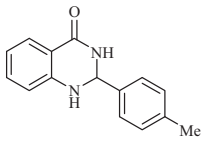
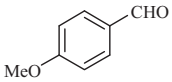
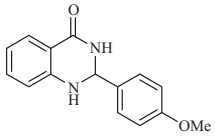
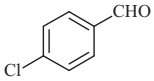
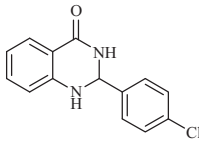
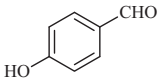
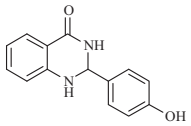
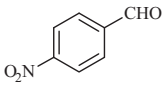
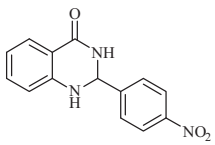
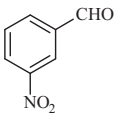
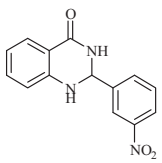
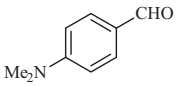
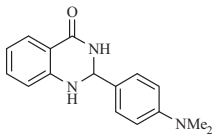
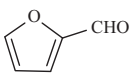
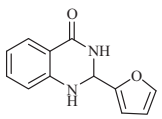
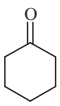
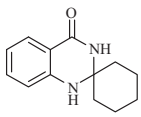
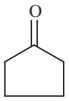
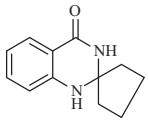
In conclusion, a new catalytic protocol to the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones has been developed. This method offers several advantages, such as use of green solvent, simple workup and purification procedure without use of any chromatographic method, mild reaction condition, use of inexpensive and commercially available starting material and short reaction time.

Table 1
Reaction of 2-aminobenzamide with benzaldehyde in the presence of various amounts of $ZrCl_4$ in various solvents.

Entry	$ZrCl_4$ (mol%)	Solvent	Time (min)	Yield[a] (%)
1	10	EtOH	7	85
2	5	EtOH	15	94
3	2	EtOH	25	95
4	1	EtOH	120	97
5	2	MeOH	25	94
6	2	CH_3CN	25	37
7	2	CH_2Cl_2	25	9
8	2	$CHCl_3$	25	9

[a] Isolated yields.

Table 2
Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by the reaction of 2-aminobenzamide with aldehydes and ketones in the presence of 2 mol% $ZrCl_4$.

Entry	Aldehyde or ketone **(2)**	Dihydroquinazoline **(3)**	Time (min)	Yield[a] (%)
1			25	95
2			15	97
3			15	93
4			37	91
5			40	89
6			20[b]	96
7			20[b]	87
8			60	82
9			9	87
10			20	92
11			50	80

[a] Isolated yields.
[b] The reactions were performed at 50 °C.

1. Experimental

All of the chemicals were commercial products. Reagent grade solvent (E. Merck) were used without purification. All melting points were obtained by Buchi B-540 apparatus. All reactions were monitored by TLC and all yields refer to isolated products. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Bruker 500 MHz spectrometer. Infrared spectra were recorded on a Bruker FT-IR Equinax-55 spectrophotometer.

1.1. General procedure for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones

To a solution of 2-aminobezamide (1 mmol) and aldehyde or ketone (1 mmol) in EtOH (3 mL), $ZrCl_4$ (4 mg, 2 mol%) was added. The mixture was stirred at room temperature for an appropriate time as indicated in Table 2. After completion of the reaction, as indicated by TLC (ethyl acetate:*n*-hexane 1:1), the product was precipitated by addition of 9 mL of water. Then the precipitate was filtered off and washed with extra water. Finally the crude product was purified by recrystallization from EtOH and water to afford the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones in 80–97% yield.

1.2. Physical and spectroscopic data for selected compound

2,3-Dihydro-2-phenylquinazolin-4(1*H*)-one (**3a**): White solid, mp 225–227° C (Lit. [7] mp 218–220° C); IR (neat) cm^{-1} ν: 3303, 3176, 3061, 1651, 1610, 1508, 1482; ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.76 (s, 1H, CH), 6.68 (t, 1H, J = 7.4 Hz, ArH), 6.76 (d, 1H, J = 8.09 Hz, ArH), 7.10 (br s, 1H, NH), 7.25 (t, 1H, J = 7.3 Hz, ArH), 7.33–7.41 (m, 3H, ArH), 7.50 (d, 2H, J = 7.44 Hz, ArH), 7.62 (d 1H, J = 7.7 Hz, ArH), 8.28 (br s, 1H, NH); ^{13}C NMR (125.7 MHz, 1H-decoupled): δ 67.4, 115.2, 115.8, 117.9, 127.7, 128.2, 129.1, 129.3, 134.1, 142.5, 148.7, 164.4.

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