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Silica Supported Zinc (II) Chloride (SiO_2-$ZnCl_2$) as an Efficient Catalyst for the Eco-Friendly Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-Ones

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ABSTRACT

Silica supported zinc (II) chloride (SiO_2-$ZnCl_2$) as an efficient and non-toxic heterogeneous catalyst have been used for the simple and facile synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones through the direct cyclo-condensation of anthranilamide and aldehydes or one-pot three-component cyclo-condensation of isatoic anhydride, ammonium acetate (or amines) and aldehydes under solvent-free conditions.

Key words: 2,3-Dihydroquinazolin-4(1*H*)-one, Anthranilamide, Isatoic anhydride, SiO_2-$ZnCl_2$

INTRODUCTION

Dihydroquinazolin-4(1*H*)-one skeletons constitute a governing class of synthetic compounds that have been long and widely employed for pharmacological properties and clinical applications. In particular dihydroquinazolin-4(1*H*)-one scaffold were found as a core unit in a number of biologically active compounds that they include anticancer, antidituric, anticonvulsant activities.[1-8] Thus, extensive efforts have been exerted on developing methodology for the synthesis of dihydroquinazolin-4(1*H*)-one derivative. Several numbers of synthetic strategies are known for the preparation of substituted dihydroquinazolin-4(1*H*)-ones.[9] Straight-forward synthesis of dihydroquinazolin-4(1*H*)-one involves the condensation of an aromatic aldehydes, and 2-aminobenzamide or three-component reactions of isatoic anhydride and ammonium acetate (or aromatic amines) with aldehydes[10-43]. Some of these procedures have certain limitations such as tedious process, long reaction times, harsh reaction conditions, and low yields.

As part of our ongoing research in the development of novel synthetic routes to the synthesis of biologically active heterocyclic compounds,[40-43] herein we report a simple and convenient method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives via direct cyclo-condensation of anthranilamide and aldehydes or one-pot three-component cyclo-condensation of isatoic anhydride, ammonium acetate (or amines) and aldehydes using Silica

supported zinc (II) chloride (SiO_2-$ZnCl_2$) as catalyst under thermal solvent-free conditions.

RESULTS AND DISCUSSION

At first, to improve the yield and optimize the reaction conditions, the reaction was carried out in the presence of isatoic anhydride, benzaldehyde and ammonium acetate in the presence of SiO_2-$ZnCl_2$ as catalyst. Then we tried to optimize the amount of the catalyst and optimal temperature for this reaction. As it was shown from Table 1, 100 °C was found to be a suitable temperature in the presence of 0.025 g of SiO_2-$ZnCl_2$ as catalyst. The results were summarized in Table 1.

Using these optimized reaction conditions, the scope and efficiency of these procedures were explored for the synthesis of corresponding 2,3-dihydroquinazolin-4(1*H*)-one derivatives (Scheme 1).

Generally, the cyclo-condensation reaction between isatoic anhydride, aryl aldehydes and ammonium acetate proceeded well and afforded the desired products (Table 2, Entries 1-10).

The effect of the nature of substituent on the aromatic ring showed no noticeable effect on this translation as they were obtained in high yields with short reaction time. Though *meta*- and *para*-substituted aromatic aldehydes gave good results, *ortho*-substituted aromatic aldehydes give product in moderate yield (Table 2; Entries 11).

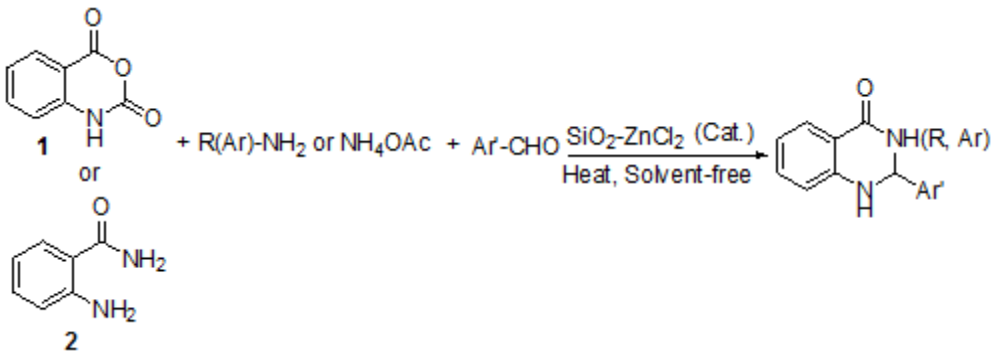
In continue, the synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1H)-ones via the reaction of isatoic anhydride, amines, and aldehydes under the optimized reaction condition was investigated (Table 2, Entries 12-17). As shown in Table 2, the reaction was compatible successfully with a variety of aldehydes and amines.

We further investigated the one-pot two-component synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzamide and aryl aldehydes (Table 2, Entries 18-27). We applied the above optimal reaction conditions (Table 1) for this reaction. As shown in Table 2, a variety of aldehydes

Table 1: Optimization amount of SiO_2-$ZnCl_2$ and reaction temperature

Entry	Catalyst (g)	T (°C)	Time (min)	Yield (%)[a]
1	0.1	100	5	84
2	0.05	100	8	86
3	0.025	100	10	88
4	0.01	100	25	81
5	0.005	100	45	71
6	0.025	80	30	70
7	0.025	r.t.	5h	-

[a]Isolated yield



Scheme 1: Preparation of 2,3-dihydroquinazolin-4(1*H*)-one derivatives

Table 2: Preparation of 2,3-dihydroquinazolin-4(1*H*)-one derivatives using SiO_2-$ZnCl_2$ as catalyst (Scheme 1)

Entry	Aldehyde	Amine	1 or 2	Product	Time (min)	Yield (%)[a]	m.p. [lit m.p. °C][ref]
1	Benzaldehyde	NH_4OAc	1	1a	7	88	217-219 [218-220][11]
2	4-Methylbenzaldehyde	NH_4OAc	1	2a	14	89	234-236 [233-234][11]
3	4-Methoxybenzaldehyde	NH_4OAc	1	3a	25	75	179-181 [178-180][11]
4	3,4-Dimethoxybenzaldehyde	NH_4OAc	1	4a	11	78	210-213 [212-214][11]
5	4-(*N*,*N*-Dimethylamino) benzaldehyde	NH_4OAc	1	5a	8	80	227-229 [228-229][15]
6	3-Fluorobenzaldehyde	NH_4OAc	1	6a	6	87	265-267 [266-267][15]
7	4-Fluorobenzaldehyde	NH_4OAc	1	7a	12	86	197-199 [199-200][15]
8	4-Chlorobenzaldehyde	NH_4OAc	1	8a	11	89	198-200 [198-200][11]
9	4-Nitrobenzaldehyde	NH_4OAc	1	9a	50	77	212-214 [213-214][15]
10	3-Nitrobenzaldehyde	NH_4OAc	1	10a	45	89	215-217 [216-217][15]
11	2-Chlorobenzaldehyde	NH_4OAc	1	11a	80	51	180-182 [1181-183][11]
12	Benzaldehyde	4-Chloroaniline	1	12a	35	74	214-216 [214-216][11]
13	4-Nitrobenzaldehyde	Ethylamine	1	13a	15	71	162-164 [160-161][11]
14	3-Nitrobenzaldehyde	Ethylamine	1	14a	17	76	176-178 [176-178][11]
15	4-Chlorobenzaldehyde	Ethylamine	1	15a	45	72	132-134 [132-135][12]
16	4-Chlorobenzaldehyde	*n*-Buthylamine	1	16a	47	70	149-151 [150-151][15]
17	4-Methoxybenzaldehyde	Ethylamine	1	17a	65	69	125-127 [124-126][12]
18	Benzaldehyde	-	2	18a	7	88	218-220 [218-220][11]
19	4-Nitrobenzaldehyde	-	2	19a	6	89	211-213 [213-214][15]
20	3-Nitrobenzaldehyde	-	2	20a	8	91	215-217 [216-217][15]
21	2-Nitrobenzaldehyde	-	2	21a	25	83	192-194 [193-194][15]
22	3-Fluorobenzaldehyde	-	2	22a	6	93	267-269 [266-267][15]
23	4-Fluorobenzaldehyde	-	2	23a	15	95	198-200 [199-200][15]
24	4-Methylbenzaldehyde	-	2	24a	12	82	234-236 [233-234][11]
25	4-Methoxybenzaldehyde	-	2	25a	14	87	179-181 [178-180][11]
26	2,4-Dimethoxybenzaldehyde	-	2	26a	30	74	187-189 [186-187][15]
27	4-Chlorobenzaldehyde	-	2	27a	9	79	197-199 [198-200][11]
28	4-*tert*-butylbenzaldehyde	-	2	28a	12	85	221-223
29	Acetophenone	-	2	29a	150	-	-

[a]Isolated yields. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.[10-39]

bearing either electron-donating or electron-withdrawing groups on the aromatic ring were investigated. However, when aromatic aldehydes with electron-donating groups are reactants, the reaction time is shorter than that with electron-withdrawing groups.

The reaction of aromatic aldehydes with nitro substituent in the presence of SiO_2-$ZnCl_2$ proceeded smoothly in high yields (Table 2, Entries 19-21). However, when acetophenone was used, the reaction was failed to give any product (Table 2, Entry 28).

The work-up procedure is very clear-cut; that is, the products were isolated and purified by simple filtration and crystallization from aqueous ethanol. Our protocol avoids the use of dry media during the reaction process, making it superior to the previous methods.

In conclusion, a reliable, rapid, and environmentally benign method for synthesizing 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones has been developed. Compared to previous reported methodologies, the present protocol features simple operations, short reaction time, environmental friendliness and good yields. Also the work-up procedure is very simple, and chromatography is not required.

EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by spectroscopic data (IR, NMR spectra) and melting points with authentic samples. The NMR spectra were recorded on a Bruker Avance DEX 400 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a JASCO FT-IR 460plus spectrophotometer. All of the compounds were solid and solid state IR spectra were recorded using the KBr disk technique. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel polygram SIL G/UV 254 plates.

General procedure

- To a mixture of isatoic anhydride (1 mmol), primary amine or ammonium acetate (1.4 mmol) and aromatic aldehyde (1 mmol) SiO_2-$ZnCl_2$ (0.025 g), were added and the mixture was stirred at 100 °C in an oil bath for the appropriate time (Table 2). After completion of the reaction which confirmed by TLC (eluent: n-hexane/ethyl acetate: 4/1), the mixture was cooled at room temperature, and then the solid was dissolved in hot EtOH. The catalyst was filtered and washed by ethanol; the filtrate solution was evaporated. Then, the solid product was purified by recrystallization procedure in aqueous EtOH (40%).
- To a mixture of 2-aminobenzamide (1 mmol) and aromatic aldehyde (1 mmol) SiO_2-$ZnCl_2$ (0.01 g), were added and the mixture was stirred at 100 °C in an oil bath for the appropriate time (Table 2). The work-up is same to up.

Selected data

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (product 8a)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.33 (s, 1H), 5.69 (s, 1H), 5.89 (s, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.91 (t, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 6.8 Hz, 1H); IR (KBr): 3305, 3056, 1654, 1610, 1489, 1155, 1051, 803, 778 cm^{-1}; Found: C, 65.11; H, 4.37; N, 10.89 $C_{14}H_{11}ClN_2O$; requires: C, 65.00; H, 4.29; N, 10.83%].

2-(4-tert-butylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (product 28a)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.28 (s, 9H), 5.74 (s, 1H), 6.67-6.77 (m, 2H), 7.04 (s, 1H), 7.26-7.65 (m, 6H), 8.23 (s. 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.5, 34.7, 67.04, 114.9, 115.6, 117.8, 126.8, 127.6, 127.9, 133.8, 139.8, 148.6, 149.5, 164.4 ppm; IR (KBr): 3306, 3054, 2965, 2927, 2867, 1653, 1612, 1489, 1155, 1051, 802, 756 cm^{-1}; Found: C, 77.23; H, 7.28; N, 10.08 $C_{18}H_{20}N_2O$; requires: C, 77.11; H, 7.19; N, 9.99%].

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