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LETTER ARTICLE

Amino Acid Catalyzed Synthesis of 2,3-Dihydroquinazolin-4(1H)-one Derivatives

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ARTICLE HISTORY

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Abstract: A simple, convenient and facile approach for the synthesis of a series of 2,3-dihydroquinazolin-4(1H)-ones in an environmentally benign method has been developed. This method involves a direct cyclocondensation of 2-aminobenzamide with aromatic aldehydes and ketones using aspartic acid as a catalyst in water.

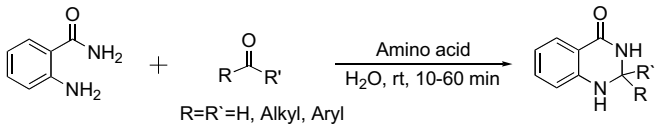
Keywords: Amino acid, catalyst, 2,3-Dihydroquinazolin-4(1H)-ones, 2-aminobenzamide, ketones, water.

1. INTRODUCTION

The compound 2,3-dihydroquinazolin-4-(1H)-one (DHQs) and its derivatives containing nitrogen heterocycles [1] as core units have pharmacological activities that attract much attention towards this. As an essential pharmacophore, quinazolinone derivatives have a variety of biological activities. Many DHQs are reported to have anticancer [2], analgesic, anticonvulsant [3], antiparkinsonian [4], antibacterial [5], diuretic [6], monoamine oxidase inhibition [7], plant growth regulation [8] and antihypertensive [9] properties. Due to their versatile biological applications, DHQ derivatives have stimulated a great interest in chemists. A variety of approaches have been developed for the synthesis of DHQs. The significant methods are (i) cyclocondensation of aldehyde or ketone with 2-amino-benzamide and (ii) reaction of isatoic-anhydride with ammonium acetate or amines, and aldehyde or ketone [10]. Several catalysts have been employed for these reactions which include heterogeneous solid catalysts Amberlyst-15, silica-$HClO_4$ [11], propylphosphonic anhydride (T3P®) [12], $CuCl_2$ [13], $ZrCl_4$ [14], $TiCl_4$/Zn [15], NH_4Cl [16], trichloroacetic acid [17], succinimide-N-sulfonic acid [18], 2-morpholinoethanesulfonic acid [19] *etc*. Recently, recyclable catalysts such as ionic liquids [20-23], metal-CNTs [24, 25], Fe_3O_4/chitosan composite nanocatalyst [26], nanocrystalline sulfated zirconia [27] and PEG-400 [28] were used.

The exploitation of amino acids as organocatalysts in asymmetric synthesis became acquainted due to their harmless, bio-renewable and low-cost nature. For instance, proline is widely used as an organocatalyst in aldol condensation [29, 30] and Ulmann reaction while tryptophan and alanine are employed in asymmetric mannich reactions [31, 32]. This prompted us to use amino acid as a catalyst in the synthesis of DHQs in water. This synthesis involves water as a solvent, which is environmental-friendly, non-volatile, nontoxic, perfectly safe and inexpensive when compared with other organic solvents.

Herein, we report our preliminary finding that aspartic acid is an efficient catalyst for the cyclocondensation reaction of DHQ synthesis in water. This is the first example for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones with amino-acid as catalyst in water (Scheme **1**).



Scheme (1). The synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives in water.

2. RESULTS AND DISCUSSION

At the commencement of our research, we investigated the model reaction between 2-aminobenzamide and benzaldehyde at room temperature with different amino acids (30 mol%) as catalysts as shown in Table **1**.

After screening nine amino acids, aspartic acid was found to be the most effective catalyst, since it resulted in the highest yield of the desired product (Table **1**, entry 7). Compared with the model reactions carried out without catalyst, the yield was very low. In addition, the amount of catalyst affected the

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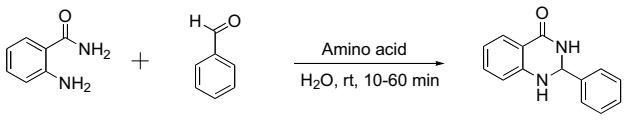
reaction significantly. We noticed that 30 mol% of aspartic acid is optimum to catalyze the reaction efficiently and further increasing the amount of catalyst decreased the yield (Table **2**, entry 7).

Table 1. The synthesis of 2,3-dihydroquinazolin-4(1H)-ones using different amino acids as catalysts.



Entry	Amino Acids	Yield (%)
1	Phenylalanine	20
2	Tryptophan	40
3	Arginine	42
4	Cystine	87
5	Glycine	88
6	Proline	71
7	Aspartic acid	95
8	Histidine	71
9	Valine	91

Table 2. The effect of mol% of aspartic acid on the model reaction.

Entry	mol% of Aspartic Acid	Yield (%)
1	5	30
2	10	33
3	15	39
4	20	47
5	25	89
6	30	95
7	35	81

In order to examine the scope and limitation of this approach, we applied these optimal reaction conditions to a variety of aldehydes and ketones. The results are illustrated in Table **3**.

Generally, the cyclocondensation reaction proceeded well and afforded the desired products in good to excellent yields. The reaction was compatible with a variety of electron-donating and electron-withdrawing substituents in the aromatic aldehydes. Steric hindrance seems to have no effect on the efficiency of this transformation. Besides aromatic aldehydes, cyclohexanone (entry 3), aliphatic aldehyde (entry 5) and heteroaryl aldehydes (entries 4 & 10) also afforded the desired product.

3. EXPERIMENTAL SECTION

All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. The NMR spectra were recorded on a Bruker 400 MHz instrument using DMSO-d_6 as the solvent. Chemical shifts (δ) are expressed in ppm with tetramethylsilane (TMS) as the internal standard and coupling constants (*J*) are reported in Hz.

3.1. Synthesis of 2,3-Dihyroquinazolin-4(1H)-one Derivatives

In a vial, 2-aminobenzamide (1 mmol), 4 mL of water, 30 mol% of amino acid (aspartic acid) were taken and stirred for 5 minutes. Then 1 mmol of aldehyde or ketone was added to the mixture and stirring was continued for 60 minutes. The progress of the reaction was monitored by TLC. After completion of the reaction, water-insoluble product was obtained. The crude products were obtained directly by filtration and washed with 20% cold ethanol. Finally, the solid product was recrystallized from ethanol-water mixture (80:20).

3.2. Spectral Characterization of Selected Compounds

3.2.1. 2-Phenyl-2,3-dihydroquinazolin-4-(1H)-one, (Entry 1, Table 3)

Yield: 95%. mp 221ºC. FT-IR (ν, cm^{-1}): 3303 (NH), 1652(C=O), 1612 (C=C), 1484 (CH_{Aro}).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.29 (br.s, 1H), 7.63 (d, 1H,), 7.51 (d, 2H), 7.41-7.35 (m, 3H), 7.26 (t, 1H), 7.11(br.s, 1H), 6.76 (d, 1H), 6.69 (t, 1H), 5.76 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 164.0, 148.3, 142.1, 133.7, 128.9, 128.7, 127.8, 127.3, 117.5, 115.4, 114.8, 67.0.

3.2.2. 2-(2-Nitrophenyl)-2,3-dihydroquinazolin-4-(1H)-one, (Entry 6, Table 3)

Yield: 90%. mp 153ºC. FT-IR (ν, cm^{-1}): 3387 (NH amine), 1669 (C=O), 1592 (C=C), 1342 (NO_2), 1486 (CH_{Aro}).

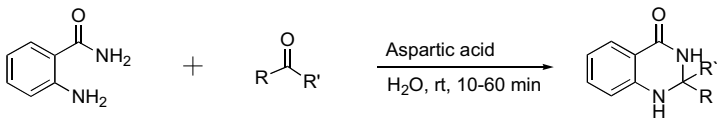
^{1}H NMR (DMSO- d_6, 400 MHz) δ 8.85 (s, 3H), 8.17 (m, 9H), 8.07 (dd, 1H), 7.92 (m, 11H,), 7.83 (m, 9H), 7.74 (d, 1H), 7.59 (m, 11H), 7.38 (m, 4H), 7.19 (m, 6H), 7.04 (d, 1H), 6.72 (m, 3H), 6.58 (d, 2H), 6.34 (t, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 190.39, 171.73, 168.03, 158072, 149.66, 149.20, 134.71, 134.64, 134.41, 134.38, 134.01, 132.78, 132.32, 132.20, 130.35, 130.28, 130.22, 119.67, 118.13, 116.83, 115.36, 114.79, 62.61.

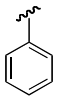
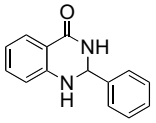
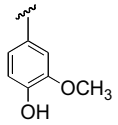
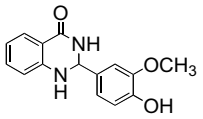
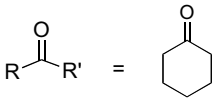
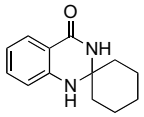
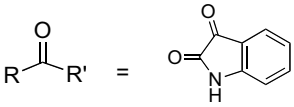
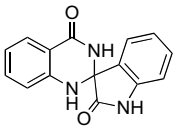
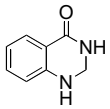
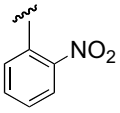
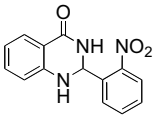
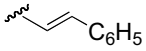
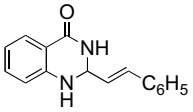
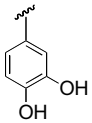
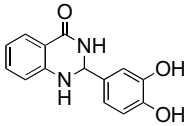
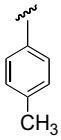
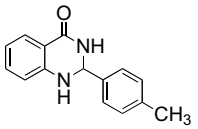
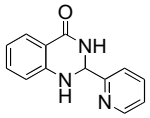
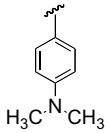
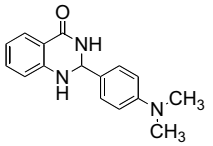
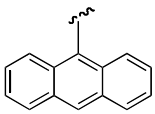
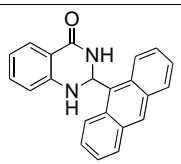
3.2.3. 2-(p-Tolyl)-2,3-dihydroquinazolin-4-(1H)-one, (Entry 9, Table 3)

Yield: 77%. mp 225ºC. FT-IR (ν, cm^{-1}): 3311 (NH amine), 1655 (C=O), 1606 (C=C), 1482 (CH_{Aro}).

^{1}H NMR (DMSO- d_6, 400 MHz) δ 8.28 (s, 1H), 7.64 (m, 1H), 7.40 (d, 2H), 7.22 (dd, 3H), 7.09 (s, 1H), 6.77 (d, 1H), 6.69 (t, 1H), 5.74 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 164.15, 148.40, 139.10, 138.20, 133.74, 129.28, 127.82, 127.28, 117.54, 115.88, 66.87.

Table 3. The synthesis of 2,3-dihydroquinazolin-4(1H)-ones using aspartic acid as catalyst.



Entry	R	R'	Product	Yield (%)	Refs.
1		-H		95	[33]
2		-H		93	[34]
3				60	[35 a-d]
4				78	[36]
5	-H	-H		94	[37]
6		-H		90	[38]
7		-H		71	[39]
8		-H		73	[40]
9		-H		77	[41]
10		-H		75	[42]
11		-H		91	[43]
12		-H		78	[44]

3.2.4. 2-(Pyridine-2-yl)-2,3-dihydroquinazolin-4-(1H)-one, (Entry 10, Table 3)

Yield: 75%. mp 185ºC. FT-IR (ν, cm^{-1}): 3423 (NH amine), 1671 (C=O), 1588 (C=C), 1448 (CH_{ben}).

^{1}H NMR (DMSO- d_6, 400 MHz) δ 8.56 (d, 1H), 8.40 (d, 1H), 7.83 (t, 1H), 7.62 (m, 1H), 7.51 (d, 1H), 7.34 (dd, 1H), 7.24 (m, 2H), 6.76 (d, 1H), 6.66 (t, 1H), 5.72 (t, 1H); ^{13}C NMR (DMSO- d_6, 100 MHz) δ 163.82, 160.72, 149.43, 137.54, 133.79, 127.71, 123.92, 120.97, 117.49, 115.11, 114.89, 67.71;

3.2.5. 2-(4-Dimethylamino)phenyl-2,3-dihydroquinazolin-4-(1H)-one, (Entry 11, Table 3)

Yield: 91%. mp 148ºC. FT-IR (ν, cm^{-1}): 3320 (NH), 1652 (C=O), 1612 (C=C), 1439 (CH_{Aro}).

^{1}H NMR (DMSO- d_6, 400 MHz) δ 8.11 (s, 4H), 7.63 (d, 4H,), 7.28 (m, 1H), 7.13 (s, 1H), 6.94 (s, 3H), 6.73 (m, 15H), 5.65 (s, 3H), 3.39 (s, 3H), 3.03 (d, 2H); ^{13}C NMR (DMSO- d_6, 100 MHz) δ 164.31, 151.15, 148.69, 133.60, 129.09, 128.18, 127.18, 117.41, 114.85, 112.40, 67.12.

CONCLUSION

In conclusion, a simple, green and effective catalytic synthetic method has been described for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones *via* the cyclocondensation of 2-aminobenzamide with aromatic aldehydes and ketone in water. Simplified operational process, easy post-treatment process and good to excellent yields are the remarkable advantages of this synthetic strategy.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

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